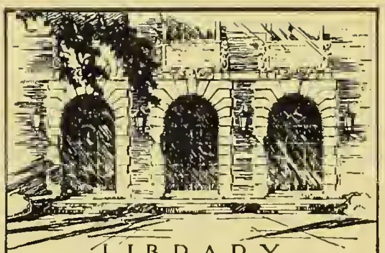

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CHEMISTRY 435 II SEMESTER 1958-1959

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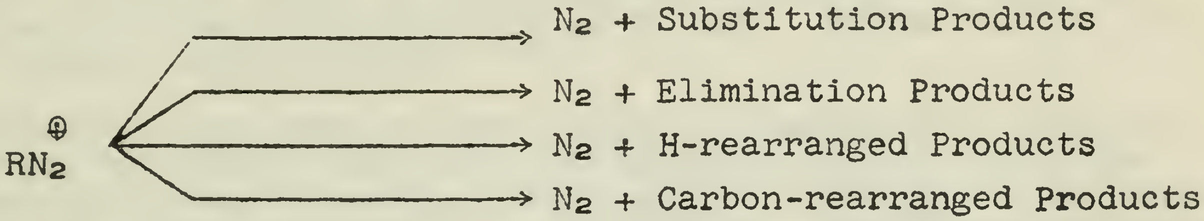
ARYL MIGRATIONS IN DEAMINATION REACTIONS

Reported by W. G. Bentrude February 16, 1959

INTRODUCTION

The probable rate-determining step in the deamination of an aliphatic amine occurs during the formation of the diazonium ion (1). The rapid decomposition of the diazonium ion may be represented by the following scheme. No general mechanism is proposed in this representation.

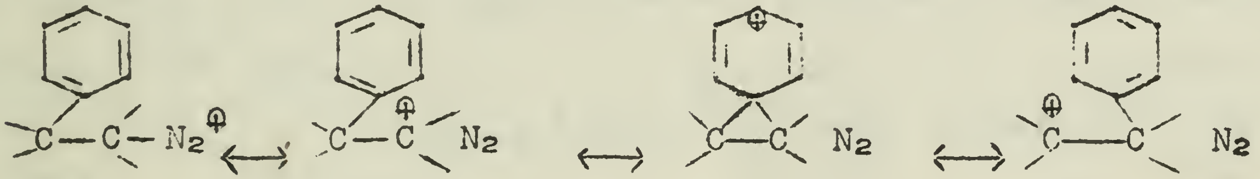

$R\overset{\oplus}{N_2}$
N_2 + Substitution Products
N_2 + Elimination Products
N_2 + H-rearranged Products
N_2 + Carbon-rearranged Products

This seminar deals with the product-determining reactions of deamination in which aryl migrations occur.

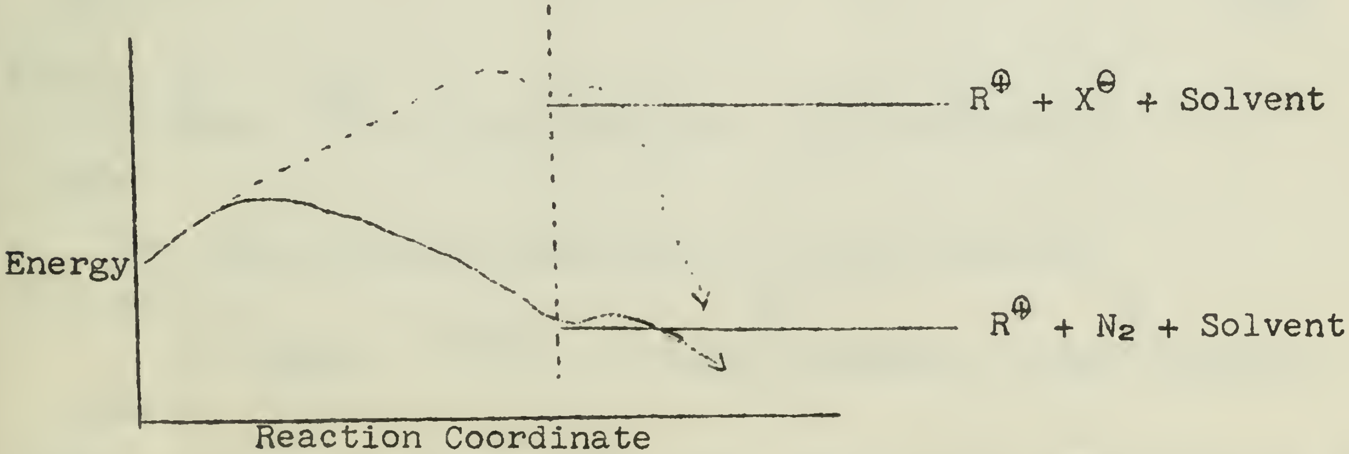
NATURE OF THE TRANSITION STATE FOR LOSS OF NITROGEN

Energetic Considerations

The transition state for the decomposition of the phenylethyl diazonium ion may be represented as a hybrid of the canonical forms I, II, III, and IV.


I II III IV

The decomposition of the alkyl diazonium ion in H_2O is a good approximation of the S_N1 or limiting mechanism. Loss of nitrogen is a very exothermic reaction. By application of the Hammond Principle (2) we would predict the energy diagram represented by the solid line in the figure (3).



The transition state for loss of nitrogen from the diazonium ion is much like the starting material, that is, structure I is of greatest

importance. One would expect very little positive charge on the carbon atom from which nitrogen is leaving. In contrast, for the reaction of R-X where X is hydroxyl, tosyl, halide, etc., represented by the dotted line, the dissociation to the carbonium ion is endothermic. The bond between the carbon and the leaving group is nearly broken in the transition state giving much carbonium-ion character to the transition state. We may then predict that:

(1) In ordinary ionizations accompanied by migration of an aryl group the migrational aptitude of the aryl group should reflect the ability of that group to stabilize the positive charge developed at the terminus. A great range of selectivity according to electron-supplying power of the aryl group should result. Ionization will be assisted by phenyl participation.

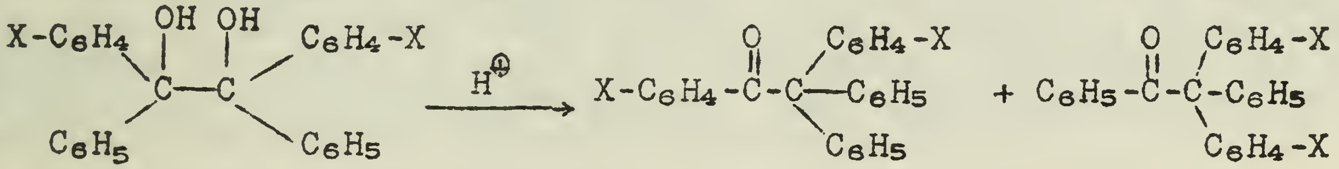
(2) Migration aptitudes of aryl groups in deamination reactions should not vary so widely with electron-supplying power, since the migration terminus should develop little positive charge in the transition state. Low aryl selectivity is predicted. Phenyl participation is not to be expected.

Migration Ratios

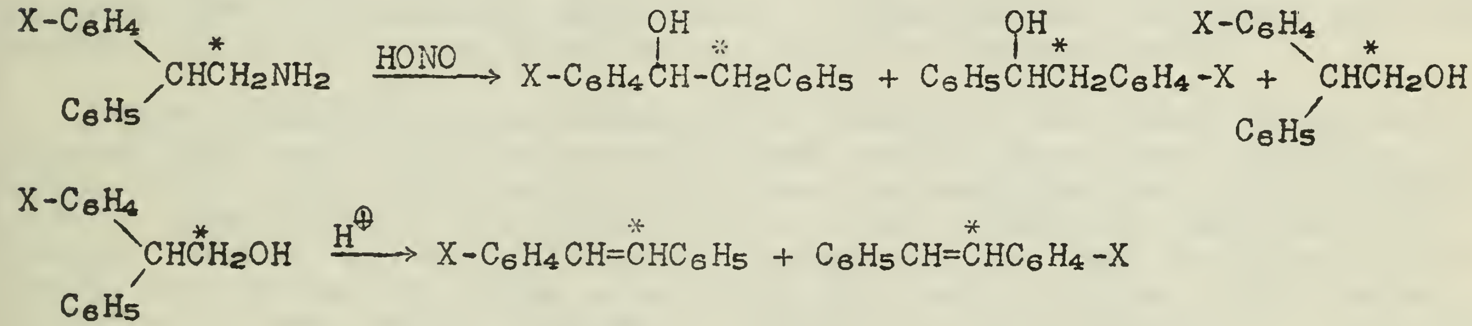
These predictions find confirmation in experimental work. We may define a migration ratio as follows:

$$\text{Migration ratio} = \frac{\text{amount of aryl migration}}{\text{amount of phenyl migration}} = \frac{\text{rate aryl migration}}{\text{rate phenyl migration}}$$

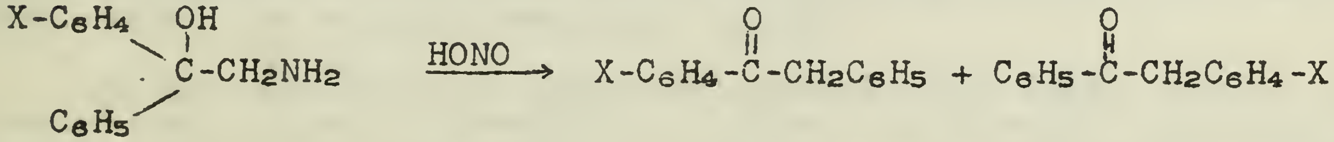
Bachmann studied the pinacolic rearrangement of substituted tetraaryl glycols (4,5). The glycols were a mixture of stereo isomers.



Burr and Ciereszko compared aryl rearrangements in the following reactions (6).



The semipinacolic deamination of amino alcohols,



studied by Curtin and Crew (8), also yielded data on migration ratios.

Migration ratios may also be determined from the data of Roberts and Regan on the deamination of arylethylamines (7).

$$X\text{-}C_6H_4CH_2\overset{*}{C}H_2NH_2 \xrightarrow{HONO} X\text{-}C_6H_4CH_2\overset{*}{C}H_2OH + X\text{-}C_6H_4\overset{*}{C}H_2CH_2OH$$

In all the reactions mentioned above, the substituent, X, is in the para position. Steric effects at the migration terminus are minimized by the lack of substitution there in all but the glycol example. The results of these studies are summarized in the following table.

Migration Ratios $\frac{\text{aryl}}{\text{phenyl}}$

Substituent X	Curtin	Burr and Ciereszko		Roberts	Bachmann
	Amino Alcohols	Amines	Alcohols	Amines	Glycols
p-CH_3O	1.56	1.5	24	1.6	500
p-CH_3	1.28	0.9(1.18)*	2	-	16
p-Cl	0.88	-	-	-	0.66

*Corrected by Collins

Although the systems are not completely analogous, it can be concluded that aryl rearrangements in deamination reactions are characterized by less selectivity than are the aryl rearrangements of the corresponding hydroxyl compounds. Several explanations have been given for this relative insensitivity.

(1) A cyclic molecular rearrangement of the diazohydroxide (10) or of the diazooxide (9).

(2) Non-cyclic rearrangement on decomposition of the diazonium ion. As predicted, the small substituent effect reflects the small amount of aryl participation in the transition state (8).

(3) Nitrogen is expelled without serious drain of the energy of the rest of the system. This should leave a relatively high-energy carbonium ion which can react on a statistical basis unless the aryl group is particularly electron-rich. This explanation, given by Burr and Ciereszko (6), is virtually the same as (2).

ROTATIONAL CONTROL OF MIGRATION

A discussion of the subject of conformational control of reaction products and its possible application to deamination reactions will be helpful prior to a consideration of possible intermediates.

When rotation is fast compared to reaction, the ratio of products formed from reaction of a compound from two different conformations depends only on the free energy difference between the two transition states and is independent of the populations of the rotational conformations. Product ratios will be affected by changes in the free energies of the transition states of either electrical or steric origin. If, however, reaction is very rapid compared to rotational interconversion, rotation becomes rate-controlling. The individual rotamers react as independent chemical species and product ratios will depend on the relative populations of the various rotational states.

The decomposition of diazonium salts is very rapid; hence, conformational control of products is a possibility worth consideration. Curtin and Wilhelm have made an estimate of the difference in free energy of activation between bromide solvolysis and deamination (11). In an effort to obtain a diazonium salt of such stability that its decomposition would become rate-determining in the deamination of the

[illegible]

In all the reactions [illegible]

[illegible]

[illegible]

*[illegible]

[illegible]

(1) [illegible]

(2) [illegible]

(3) [illegible]

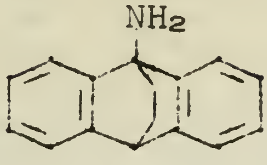
[illegible]

[illegible]

[illegible]

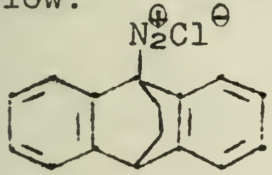
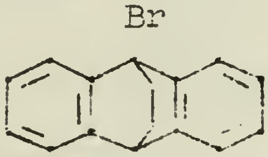
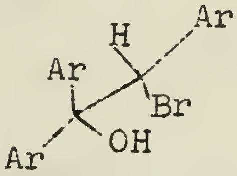
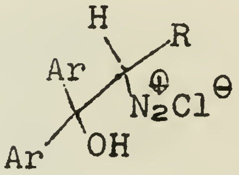
[illegible]

amine or be so slow that the diazonium salt could be isolated, amine I was synthesized.



I

Deamination at -70° gave complete reaction in less than 15 seconds. A minimum value of the rate constant for the decomposition of the diazonium ion was calculated. A comparison of the rate and free energy of activation for this decomposition with known values is given below.

k $> 10^{-2}$ sec^{-1} k $< 10^{-25}$ sec^{-1} $\Delta F^{\ddagger} =$ 26-27 kcal.(12) V

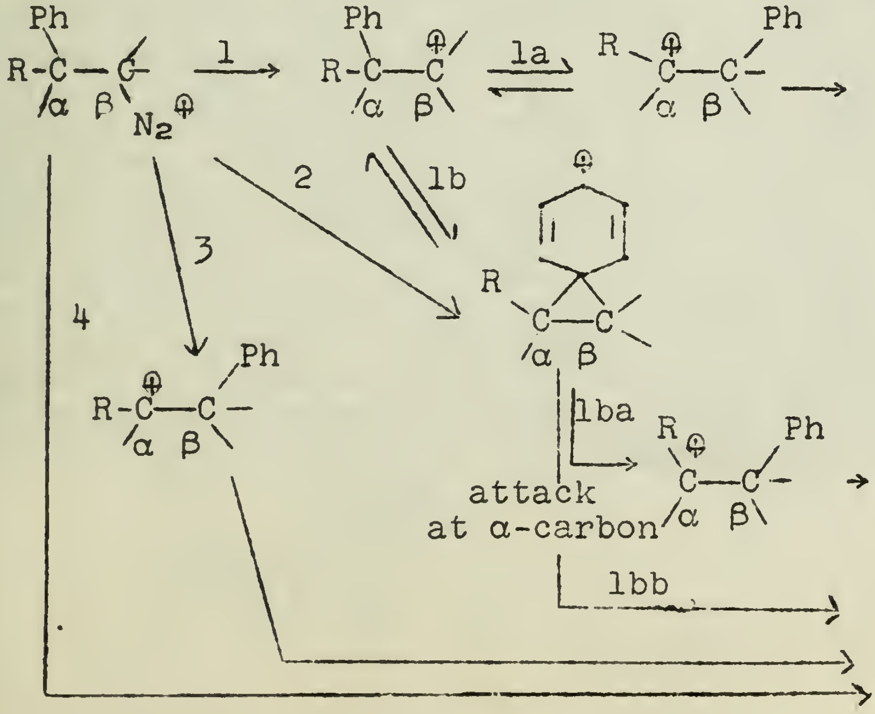
Ia II IV

$\Delta\Delta F^{\ddagger}$ 21 kcal. (Ia – II)

Very little is known of the barriers to rotation about carbon-carbon single bonds. The barrier for butane passing from one skew conformation to the other is estimated to be in the range 3.6-5.3 kcal. (13,14). From these figures, $\Delta F^{\ddagger}$ for decomposition of the diazonium salt V corresponding to bromide IV would be 5-7 kcal. Assuming the barriers to rotation to be somewhat greater in V than in butane, say 6-8 kcal., it seems reasonable that the rate of the slowest step in the product-determining reactions of the diazonium ion, V, might now be faster than rotation. Migration would be even more rapid than this slow step. Rotational control of the products of this deamination would not be an unreasonable prediction.

INTERMEDIATES IN ARYL MIGRATION DURING DEAMINATION

The possible pathways by which aryl migration may proceed during deamination are represented below.



Configuration of products of the β-carbon:

1 → 1a
Inverted or retained, depending upon the relative rates of migration and carbon-carbon bond rotation

1 → 1b → 1ba
Same as 1 → 1a

2 → 1ba
inversion

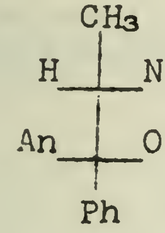
1 → 1b → 1bb
same as 1 → 1a

2 → 1bb
inversion

3 and 4
inversion

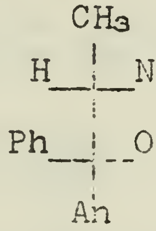
Several authors have studied the question of intermediates. Of particular interest has been the question of whether open or bridged carbonium-ion intermediates are involved. Normally, one would expect the participation of a phenonium ion during dissociation to be profitable only when the transition state for rearrangement has considerable carbonium-ion character. Then one would expect loss of nitrogen to give a classical open carbonium ion which might then rearrange an aryl group by way of a phenonium-ion intermediate.

In an extension of the work on the semipinacolic deamination reaction to amino alcohols substituted at the migration terminus, Curtin and Crew studied the migration products of racemic erythro- and threo-1-p-anisyl-1-phenyl-2-amino-1-propanols VI. The products of the deaminations were the ketones VII and VIII (15).



+ enantiomer

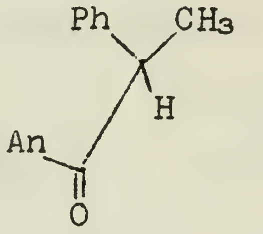
dl-erythro



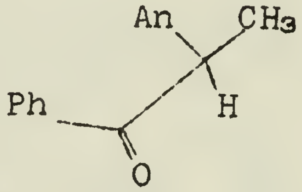
+ enantiomer

dl-threo

VI



VII



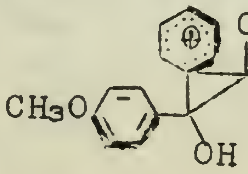
VIII

The products of the deamination as determined by ultraviolet analysis were

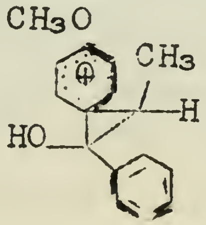
erythro VI → 88% VII + 12% VIII

threo VI → 5.8% VII + 94.2% VIII

The fact that the erythro isomer rearranges less specifically than the threo isomer was explained by assuming an electrical factor, E, the ratio of anisyl to phenyl migration in the absence of steric effects and a steric factor, S, the same ratio for the threo isomer in the absence of electrical effects. The values E = 1.49 ± 0.04 and S = 10.9 ± 0.3 were obtained. Demonstration that the configuration of the terminus is largely inverted in one case (16) plus the fact that a high degree of retention of optical activity accompanies the rearrangement of closely related amino alcohols (17) led the workers to postulate migration simultaneously with or immediately after the elimination of nitrogen. The steric factor, S, was explained in terms of the so-called "cis effect" which destabilizes the transition state. The destabilization is probably due to a composite of effects including steric strain as shown in structure IX below. Here IX and X represent the assumed transition states for trans migration of the phenyl or anisyl group in the threo isomer.



IX

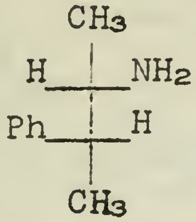


X

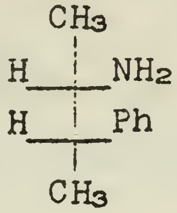
In the case of the threo isomer, both factors work in favor of anisyl migration, but the steric factor favors phenyl migration in opposition to the electrical factor in the erythro case.

Cram studied the deaminations of L(+)-threo-3-phenyl-2-butylamine, XIa, and the L(+)-erythro-3-phenyl-2-butylamine, XIb (18).

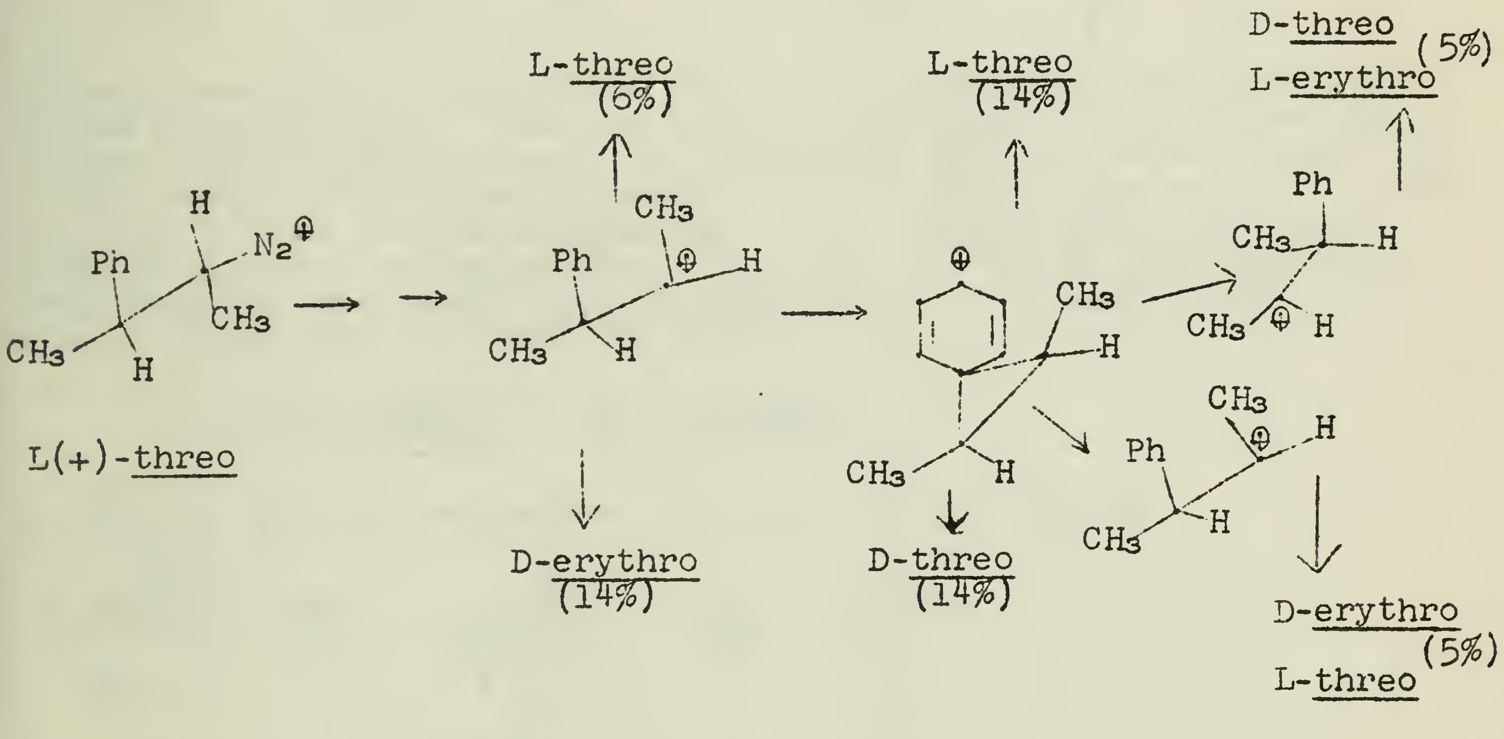
XIa



XIb



The alcoholic products of the deamination of XIa where phenyl migration is involved were explained by the following:



In addition, the relative amounts of migration, methyl:phenyl:hydrogen: 32:24:24 are what would be predicted on consideration of the relative populations of the conformations of the threo amine. In addition no cis effect was found in solvolysis of the corresponding tosylate. The following postulations arose from these observations.

(1) The first step is probably the formation of the diazonium ion.

(2) The diazonium ion dissociates to a nitrogen molecule and a carbonium ion. The driving force for loss of nitrogen comes from the formation of nitrogen and not from neighboring-group or solvent participation.

(3) The neighboring group or solvent becomes involved only after formation of a very high-energy, little-solvated, very short-lived, open carbonium ion.

(4) The high-energy carbonium ion gives product by conformational control with no electronic or cis effect being important.

(5) Even though the transition state for loss of nitrogen and migration are not the same, trans migration will predominate, because the group trans to the leaving nitrogen is the group eclipsed with the empty p-orbital of the carbonium ion.

(6) Both classical open-ion and phenonium-ion intermediates are important.

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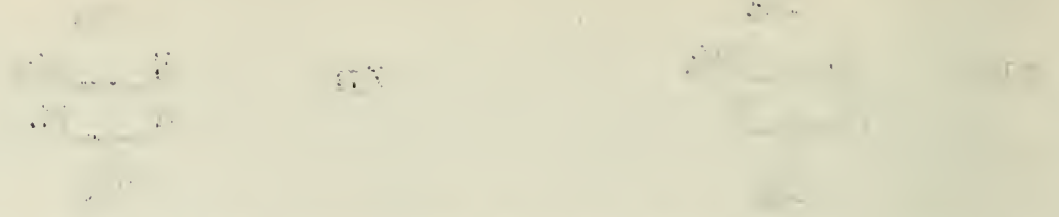

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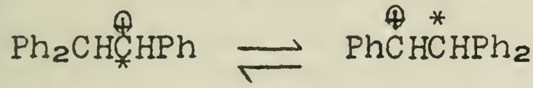
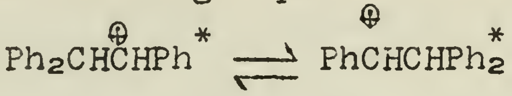
Evidence for classical open-ion intermediates for the migration of phenyl groups has been presented by Bonner and Collins (19). Chain- and ring-labelled 1,2,2-triphenylethylamines, XII, were deaminated at 5° C. and the distribution of label in the product, 1,2,2-triphenylethanol, isolated in 96% yield, was determined. The existence of open-ion intermediates was deduced by comparison of the C^{14} label position in the products with that predicted by kinetic considerations. Assume that the phenyl migration proceeds through open ions.

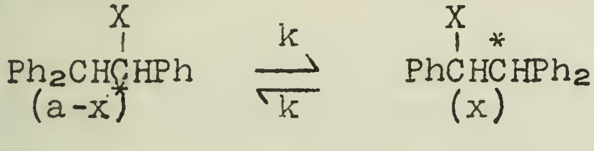
1) 

$$Ph_2CH\overset{\oplus}{\underset{*}{C}}HPh \rightleftharpoons Ph\overset{\oplus}{C}H\overset{*}{C}HPh_2$$

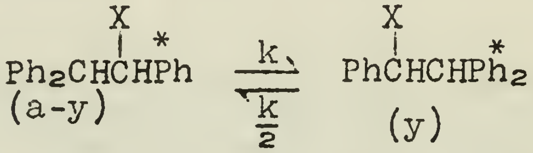
2) 

$$Ph_2CH\overset{\oplus}{C}HPh^{*} \rightleftharpoons Ph\overset{\oplus}{C}HCHPh_2^{*}$$

Consider the following process representing chain-and ring-labelled equilibration in the triphenylethyl system.

3) 

$$\underset{(a-x)}{Ph_2CH\overset{X}{\underset{*}{C}}HPh} \underset{k}{\overset{k}{\rightleftharpoons}} \underset{(x)}{Ph\overset{X}{C}H\overset{*}{C}HPh_2}$$

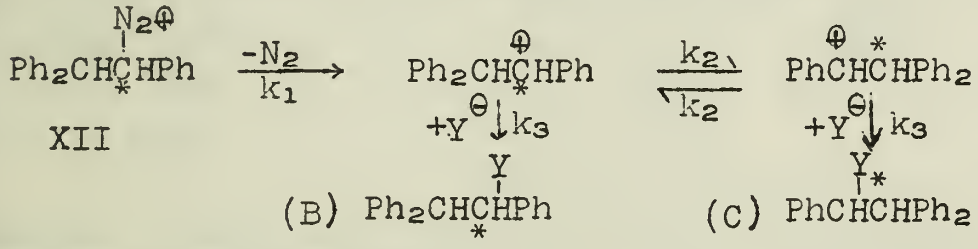
4) 

$$\underset{(a-y)}{Ph_2CH\overset{X}{C}H\overset{*}{Ph}} \underset{\frac{k}{2}}{\overset{k}{\rightleftharpoons}} \underset{(y)}{Ph\overset{X}{C}HCH\overset{*}{Ph_2}}$$

It is assumed that each phenyl group on a tertiary carbon has equal chance for migration. This is true for migration through open ions but not true if phenonium-ion intermediates are involved. Value (a) is the amount of original unequilibrated triphenylethylamine. Values (x) and (y) are the concentrations of rearranged chain- and ring-labelled isomers, respectively. Processes 3) and 4) then represent the classical open carbonium-ion equivalent of internal return. A kinetic treatment of 3) and 4) yields

$$5)\quad \frac{1}{2}\log\frac{0.500}{0.500-x} = \frac{2}{3}\log\frac{0.667}{0.667-y}$$

A specific open-ion mechanism for deamination would be



$$\underset{XII}{Ph_2CH\overset{N_2^{\oplus}}{\underset{*}{C}}HPh} \xrightarrow[k_1]{-N_2} Ph_2CH\overset{\oplus}{\underset{*}{C}}HPh \underset{k_2}{\overset{k_2}{\rightleftharpoons}} Ph\overset{\oplus}{C}H\overset{*}{C}HPh_2$$

$$Ph_2CH\overset{\oplus}{\underset{*}{C}}HPh \xrightarrow[k_3]{+Y^{\ominus}} (B)\ Ph_2CH\overset{Y}{\underset{*}{C}}HPh \qquad Ph\overset{\oplus}{C}H\overset{*}{C}HPh_2 \xrightarrow[k_3]{+Y^{\ominus}} (C)\ Ph\overset{Y}{C}H\overset{*}{C}HPh_2$$

The final concentrations of isomerized products are B and C. Kinetic considerations yield:

$$6)\quad \frac{B}{C} = 1 + \frac{k_3}{k_2}$$

Application of these considerations to the ring-labelled isomer gives similarly

$$7)\quad \frac{B'}{C'} = \frac{1}{2} + \frac{k_3}{k_2}$$

where B' and C' represent the final concentrations of isomerized products in the ring-labelled case. Simultaneous solution of 6) and 7) leads to

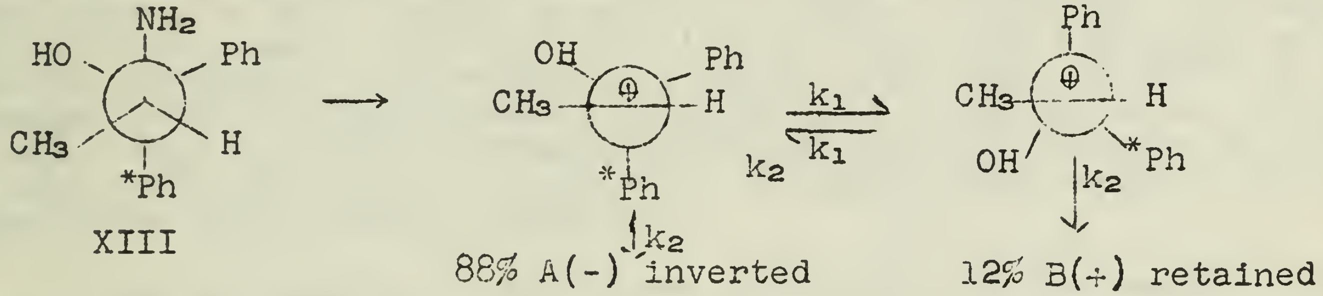
$$8)\quad \frac{1-2C}{C} = \frac{2-2C'}{2C'}$$

which represents dissociation without internal return through open-ion intermediates. Equations 5) and 8) represent the limiting or boundary conditions for phenyl migration through classical open-ion intermediates. The data for the deamination of XII and other reactions of the triphenylethyl system are summarized below. R is the 1,2,2-triphenylethyl group.

Reaction	Experimental	Predicted		Experimental			
	y and C'	X	C	X	dev.	C	dev.
Deamination of R-NH_2	31.8	29.0	27.4	28.2	+0.8	27.4	-0.8
Hydrolysis of R-tosylate	23.6	22.2	21.1	22.2	0	21.1	-1.1
Acetolysis of R-tosylate	47.1	40.3	38.1	39.5	+0.8	38.1	-1.4
Dehydration of R-OH	60.2	47.7	46.3	47.9	-0.2	46.3	-1.6

Since the results fell within limits predicted by equations 5) and 8), Collins and Bonner have postulated migration of the phenyl group in the triphenylethyl system by way of classical open ions to be the simplest mechanism. That interconversions 1) and 2) proceed through bridged ions cannot be excluded but only complicates the mechanism unnecessarily.

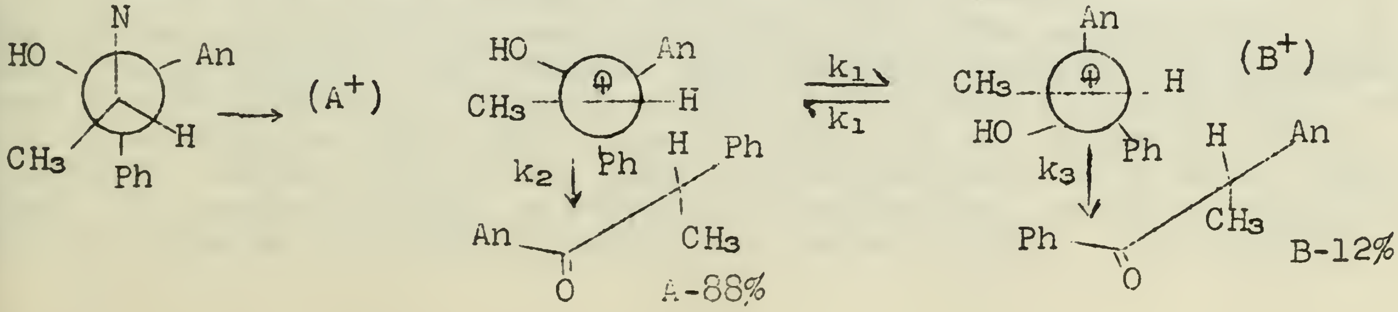
Collins extended the labelling studies to specifically labelled 1,1-diphenyl-2-amino-propanol, XIII. Deamination resulted in phenyl migration to give ketone products. All labelled phenyl migrated to give product which was inverted at the migration terminus, whereas all unlabelled phenyl migration was characterized by retention of terminal configuration. The ratio of percentage inversion to percentage retention was 88 to 12. These results were explained by a mechanism which involves a non-concerted phenyl migration after the formation of a classical open carbonium ion. Migration of unlabelled phenyl occurs from the same side as nitrogen leaves. No eclipsing of phenyl and methyl groups need occur and no cis effect need be involved to explain the lower amount of migration of unlabelled phenyl compared to labelled phenyl. Migration is considered to be fast compared to rotation. Products are conformationally controlled. The mechanism given is:



Similar results are found for phenyl-labelled 1,1,2-triphenyl-2-amino-1-ethanol. These findings are in opposition to Cram's statement that "neighboring substituents must still approach the face of the carbon atom opposite that from which nitrogen left". Only the most stable conformation of the diazonium ion is considered.

No attempt has been made by Collins to explain the results obtained by Curtin on the deamination of the diastereoisomers of 1-p-anisyl-1-phenyl-2-amino-1-propanol, VI, mentioned previously. It would seem profitable to attempt a kinetic treatment to explain the product ratios.

Consider the reaction mechanism for the erythro isomer of VI.



where A and B are the percentages of the ketones shown formed. Then

$$9)\quad \frac{d[A]}{dt} = k_2[A^{\oplus}] \quad , \quad \frac{d[B]}{dt} = k_3[B^{\oplus}]$$

Steady state considerations lead to

$$10)\quad \frac{d[B^{\oplus}]}{dt} = k_1[A^{\oplus}] - k_1[B^{\oplus}] - k_3[B^{\oplus}] = 0$$

Substitution of $[A^+]$ and $[B^+]$ from 9) and 10) followed by integration leads to the relationship

$$11)\quad B = \frac{k_3}{k_2}\left[\frac{k_1}{k_1 + k_3}\right]A$$

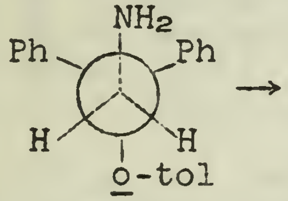
For the erythro isomer the percentage of product A from phenyl migration is known to be 88, the percentage of product B to be 12. The electrical effect for the ratio of anisyl to phenyl migration in the absence of steric factors was determined by Curtin to be approximately 1.5 (8,15). Hence we may assume

$$12)\quad \frac{k_{An}}{k_{Ph}} = \frac{k_3}{k_2} = 1.5$$

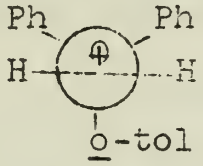
Since A is 88 and B is 12, it follows from 11) and 12) that for the erythro isomer $k_3 = 10.5\ k_1, \quad k_2 = 7.0\ k_1$

In the threo isomer, the phenyl and anisyl groups will have changed positions and in an equilibrium such as is shown for the erythro isomer, k_3 will become k_2 and vice versa. All other considerations are the same. By equation 11) we predict that the threo isomer will be deaminated to give 8% A and 92% B. This prediction is in good agreement with the experimental findings: 6% A and 94% B are actually formed. Thus open-ion intermediates which rearrange to give products by conformational control may be used to explain the products of this competitive anisyl-phenyl migration.

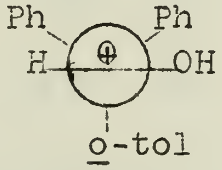
A similar explanation was given by Collins for the results of comparisons of competitive migrations in the 2,2-diphenyl-2-o-tolylethylamine, XIV, and diphenyl-o-tolylacetaldehyde, XV, systems. Deamination of XIV and treatment of XVI with concentrated sulfuric acid should give similar carbonium ions, XIVa and XVa. In both cases o-tolyl migration would be expected to lead to greatest relief of strain and to predominate over phenyl migration.



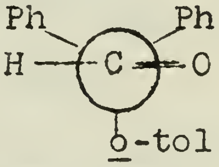
XIV



XIVa



XVa



XV

The ratios of o-tolyl to phenyl migration for XIVa and XVa were 0.8 and 3 respectively. The results from XVa were explained by assuming that the carbonium ion is sufficiently stabilized by the hydroxyl group and by solvent to allow rapid equilibration of the rotamers before migration, which leads to the expected predominance of o-tolyl migration. In contrast, XIVa, a primary carbonium ion, would be very unstable, leading to rapid migration of the aryl group. The migration

ratio is explained by consideration of relative populations of the amine XIV superimposed on a rate preference for o-tolyl.

Unsymmetrical bridged carbonium ions have been postulated by Roberts and Regan for the migration of aryl groups during the deamination of arylethylamines labelled at the 1-position by C^{14} (7).

Treatment of the series of 2-(-4-substituted)-phenylethylamines with nitrous acid in water and in acetic acid was found to yield varying amounts of isotope position rearrangement products. The substituents were $-OCH_3$, -H, and $-NO_2$. The most rearrangement (45%) was observed in acetic acid with the substituent $-OCH_3$ and the least (5%) when the substituent was $-NO_2$ in water or in acetic acid. The results were rationalized on the basis of interconvertibility of the unsymmetrical ions as a function of the ability of solvent and substituent groups to stabilize a symmetrical intermediate or transition state through which the unsymmetrical ions were to be interconverted. In view of the work of Collins since the time of this publication, a mechanism involving open ions which are interconverted seems more plausible.

* *

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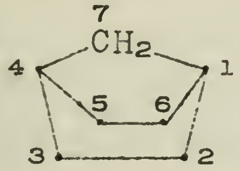
Since the completion of this abstract, stereochemical evidence for the existence of only open-ion intermediates in the deamination of 1,2,2-triphenylethyl amine has been published.

22. C. J. Collins, W. A. Bonner and C. T. Lester, J. Am. Chem. Soc., 81, 466 (1959).

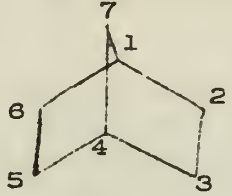
REACTIONS AT THE 7-POSITION OF THE BICYCLO-[2.2.1]HEPTANE SYSTEM

Reported by D. E. Gwynn February 23, 1959

Bicyclo[2.2.1]heptane is best thought of as the boat form of cyclohexane with a 1,4-methylene bridge (I) designated as carbon number seven. It is more conveniently drawn as structure II. Bicyclo-[2.2.1]heptane is commonly referred to as norbornane but abstracted as norcamphane.

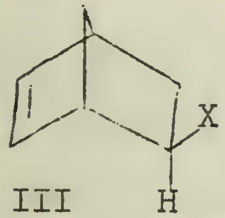


I

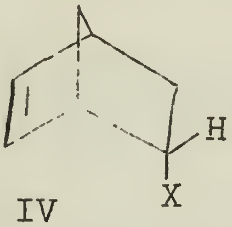


II

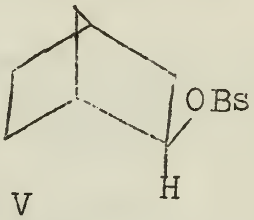
Some early studies (1-7) of the norbornane (norcamphane) system were concerned with solvolytic reactivities of exo- and endo-5-substituted-norbornene derivatives (III and IV respectively) as compared



III

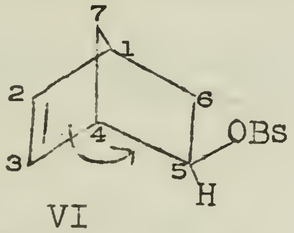


IV

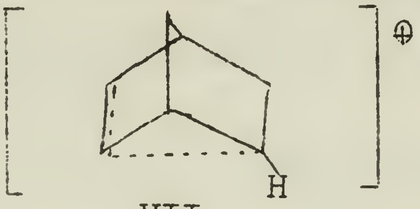


V

with the saturated derivatives of III and IV. It was found that exo-5-dehydronorbornyl brosylate (III, X = -OBs) is solvolyzed on the order of 7000 times as rapidly as is the endo-isomer (IV, X = -OBs) and about twice as fast as exo-2-norbornyl brosylate (V). This enhanced rate of ionization suggested the existence of an important interaction between a carbonium ion center and the π-electron cloud of the C-2, C-3 double bond as shown in VI. This interaction can give rise to a non-classical ion hybrid (VII) resulting from the delocalization of the olefinic electron cloud in the rate determining step.

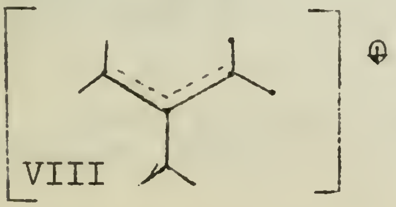


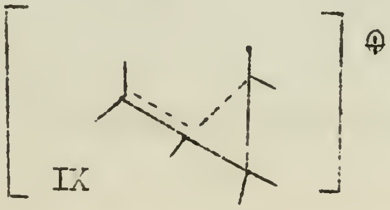
VI



VII

Cation VII has been termed "homoallylic" by Winstein (8) since it can be thought of as the next homolog of the allylic carbonium ion hybrid VIII, with a methylene group interposed as shown in IX.





When the 7-norbornenyl (dehydronorbornyl) derivatives were investigated, similar evidence of "anchimeric assistance" was found.

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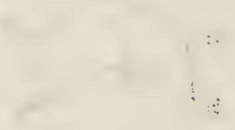

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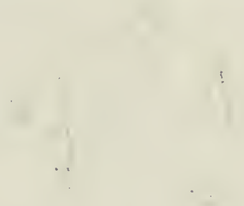

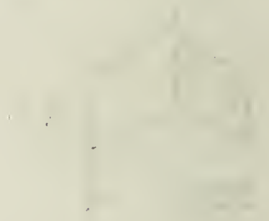

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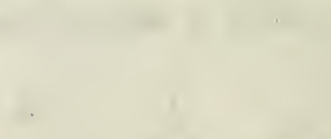

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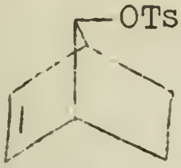
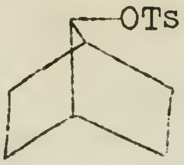
Thus the solvolytic reactivity of the favorably oriented anti-7-norbornenyl tosylate (X) was about 10^{11} times greater than that of the 7-norbornyl tosylate (XI) (9).



X

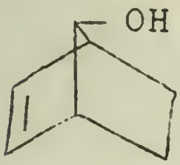
k_1 (25°)
9.04×10^{-4} sec^{-1}



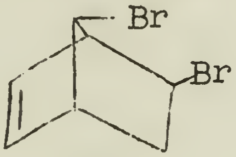
XI

k_1 (25°)
6.36×10^{-15} sec^{-1}

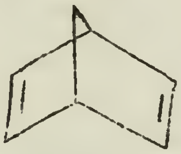
The corresponding alcohols of X and XI were prepared by the following method. Anti-7-norbornenol (XII) was first obtained as its acetate by reaction of ethylene with acetoxycyclopentadiene at 190° and secondly by selective hydrolysis of exo-5-anti-7-dibromonorbornene (XIII), one of the products of addition of bromine to bicycloheptadiene (XIV), followed by zinc debromination of the resulting bromohydrin XV. 7-Norborneol (XI) was obtained by catalytic hydrogenation of XII.



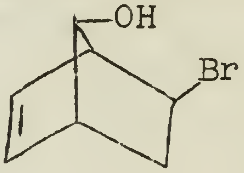
XII



XIII

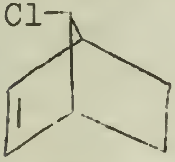


XIV

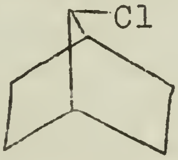


XV

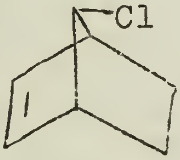
Roberts and his co-workers (10) had mentioned earlier that syn-7-chloronorbornene (XVI) and 7-chloronorbornane (XVII) were exceptionally unreactive compared with cyclopentyl chloride in 80% ethanol. Later these workers (11) measured the solvolysis rates of the following series of chlorides (XVI-XX):



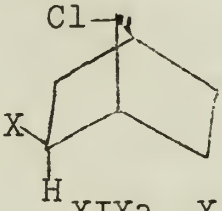
XVI



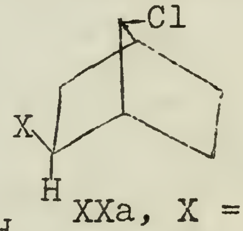
XVII



XVIII



XIXa, X = OH
b, X = OCH_3



XXa, X = OH
b, X = OCH_3

Table I. Solvolysis Rates of Chlorides in Aqueous Ethanol at 99.7° C.

Chloride	vol. % EtOH	~~vol~~ rel. k_1
syn-7-Norbornenyl (XVI)	50	< 0.01
7-Norbornyl (XVII)	50	< 0.005
anti-7-Norbornenyl (XVIII)	50	1900
	80	7
exo-Norbornyl	80	0.13
Cyclopentyl	50	1.0

These bicyclic compounds were prepared by the following reaction sequence (10):

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[illegible]

[illegible]

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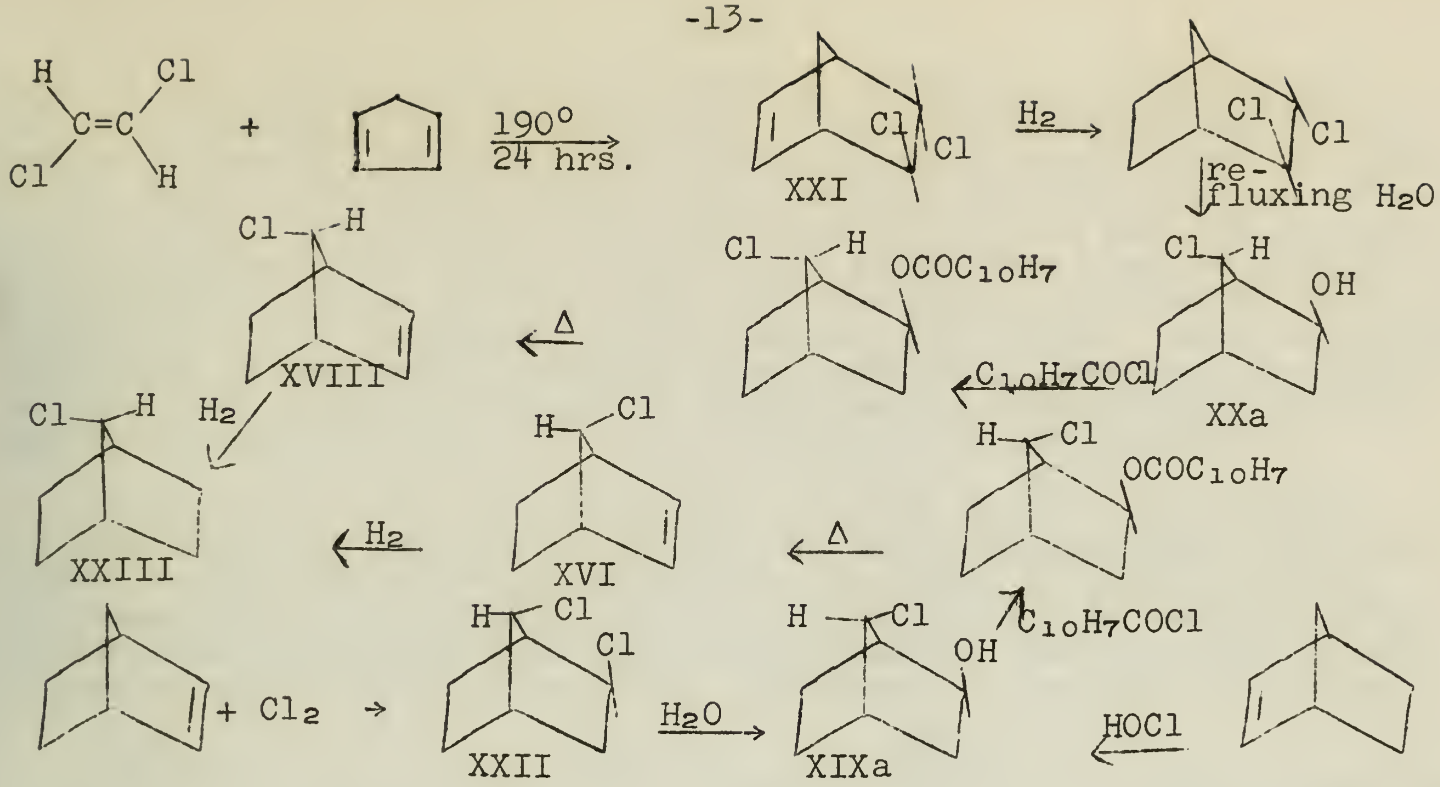
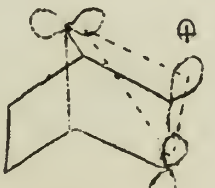


The trans-configuration of XXI was confirmed by dipole measurements. Hydrolysis of the saturated dichloride obtained from hydrogenation of XXI gave a chlorohydrin (XXa) different from the one obtained from hydrolysis of exo-2-syn-7-dichloronorbornane (XXII). The corresponding olefins, anti-7-chloronorbornene (XVIII) and syn-7-chloronorbornene (XVI) respectively, yielded an identical product upon hydrogenation, namely 7-chloronorbornane (XXIII).

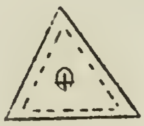
The solvolysis rates of the chloroethers and chlorohydrins (XIXb and XXb, XIXa and XXa) were measured in expectation of showing a neighboring group participation effect from the favorably situated hydroxyl and methoxy groups. However, both of these compounds were found to have very unreactive chlorines as no reaction was observed in 80% ethanol at 85° for 24 hrs. The chlorohydrins did react slowly in the presence of a slight amount of base. The syn-chlorohydrin appeared to react about 5.5 times more slowly than the anti-isomer. Such a small rate difference would seem to indicate that direct oxygen participation in the rate determining step was not very important.

Both studies have shown the much greater degree of reactivity associated with the anti-7-norbornenyl derivatives as compared with the syn-7-norbornenyl and 7-norbornyl compounds.

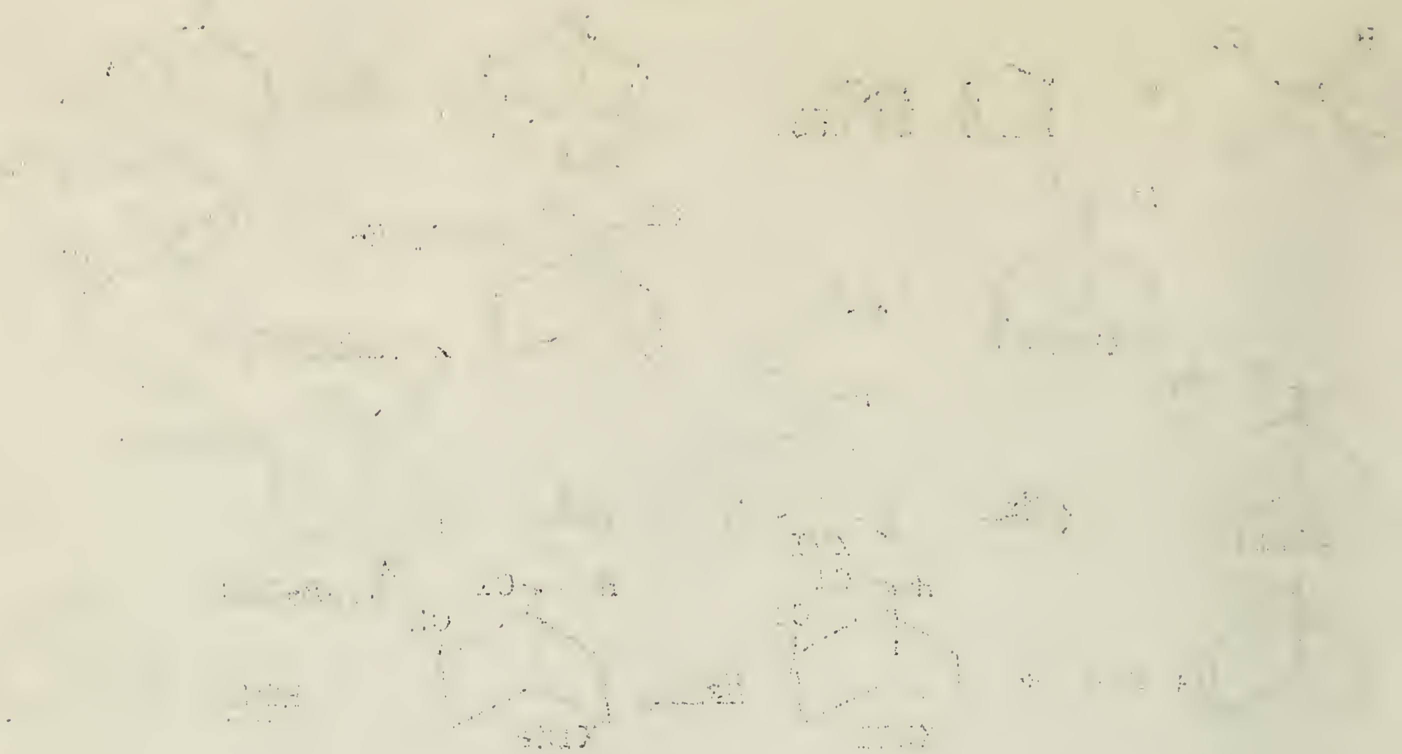
The high degree of reactivity as explained by Winstein, Woodward and their co-workers (9,12) is attributed to the "anchimeric assistance" to ionization at C-7 involving the C-2,3 π-electron cloud which then results in the intermediate cation XXIV. This cation can be likened to the previously mentioned 5-norbornenyl cation (VII) and thus thought of as another "homoallylic" case. Woods, Carboni and



XXIV



XXV



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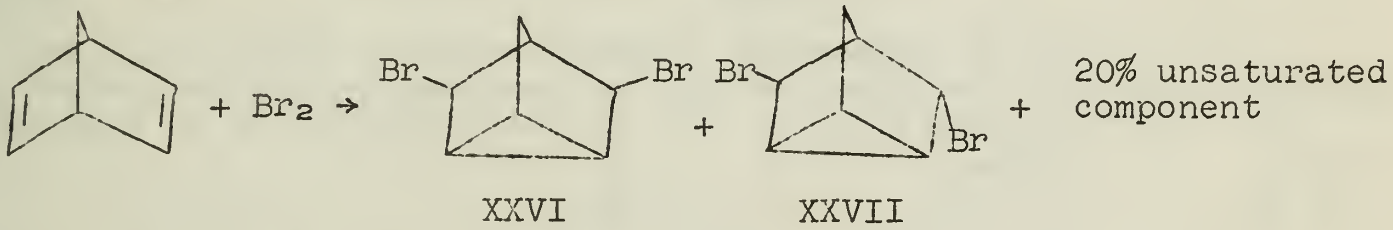
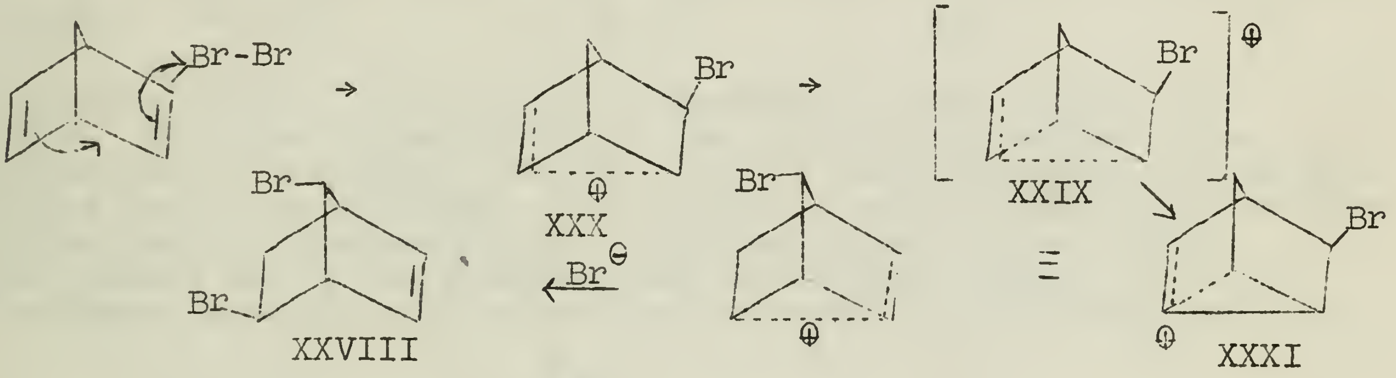
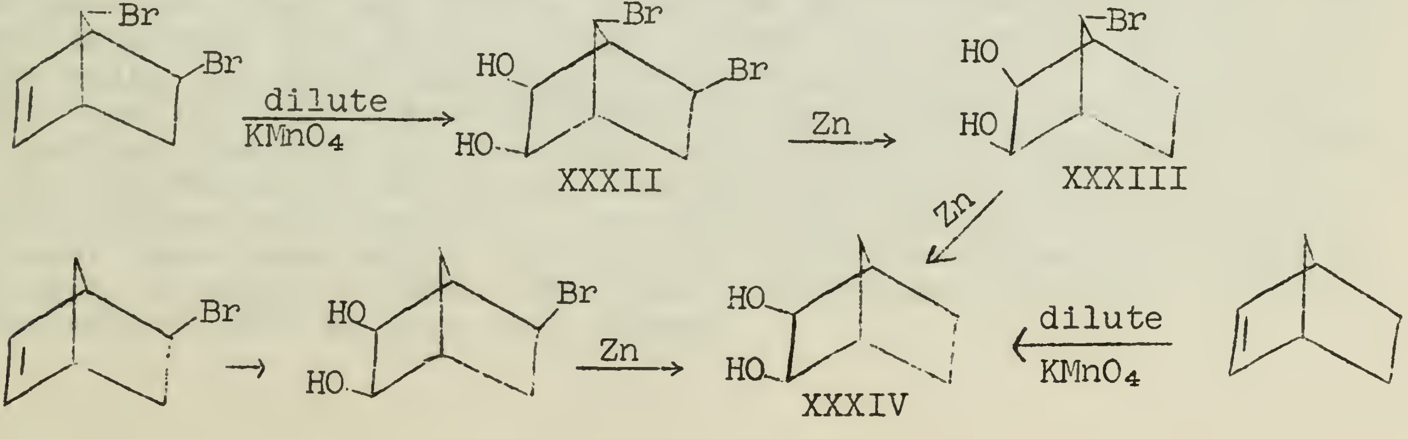
Roberts (11) described structure XXIV as a "bis-homocyclopropenyl" cation to emphasize its relationship to the cyclopropenyl cation XXV. Such a cation is predicted by simple molecular orbital theory to have a very stable π-electron system. The maximum net stabilization energy due to orbital overlap for XXIV was found to be 10.5 kcal as computed by molecular orbital theory. This value approaches that calculated for the allyl cation of 16.6 kcal. and is quite a bit greater than the value of 7.2 kcal computed for the homoallylic cation. Such an energy difference is consistent with the rate data which show anti-7-norbornenyl chloride (XVIII) solvolyzing approximately 110 times as fast as exo-norbornenyl chloride (III, X = Cl) at 85° in 80% ethanol.

Winstein in later investigations (12,13) studied the products obtained from the addition of bromine to bicycloheptadiene. This reaction yielded 20% unsaturated product (as shown by hydrogenation), which was shown to be highly reactive in comparison to the saturated dibromotricyclenes XXVI and XXVII also obtained, and 23 times as reactive as exo-5-bromonorbornene in 80% ethanol. The only structure compatible with the chemical evidence was XXVIII, the formation of which was rationalized by the mechanism shown, with cation XXIX being either an intermediate or transition state in going from XXX to XXXI.





The high reactivity of XXVIII was found to disappear on conversion of the olefinic linkage to the glycol (XXXII). This glycol when treated with zinc in alcohol yielded first a monobromoglycol XXXIII different from the one obtained from exo-5-bromonorbornene. Further



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treatment with zinc of either of the two monobromoglycols gave a completely debrominated glycol which proved to be identical with *exo-cis*-2,3-dihydroxynorbornane (XXXIV) prepared from treatment of norbornene with cold dilute permanganate (14).

Solvolysis rates of some norbornenyl derivatives were measured and are given in Tables II and III.

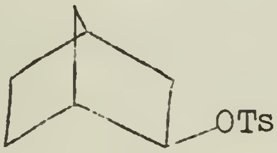
Table II. - Comparison of Rates of Solvolysis of Some Norbornenyl Chlorides in 80% Ethanol

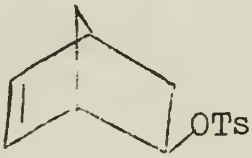
Chloride	rel. rate at 25°
exo-5-	1
exo-5-anti-7-	14
endo-4-*exo*-5-	6.3×10^{-3}
endo-4,5-	2.2×10^{-4}

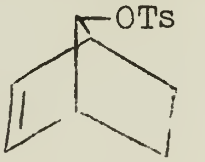
Table III. Comparison of Rates of Acetolysis of Some Norbornenyl Tosylates

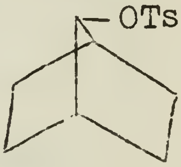
Tosylate	rel. rate at 25°
exo-5-bromo-*anti*-7-	1×10^{4}
anti-7-	2×10^{5}
exo-5-	8×10^{3}
endo-5-	1

The full extent of the anchimeric assistance to ionization of *anti*-7-norbornenyl derivatives can best be realized from the following comparisons of acetolysis rates at 25° compiled from previous data.



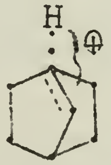






rel. rates 2×10^{9} 4×10^{9} 10^{11} 1

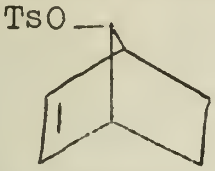
The striking factor is the extreme inertness of the 7-norbornyl tosylate. This can be explained by the unfavorable geometry for stabilization of a cationic center at C-7. Thus any hyperconjugative resonance involving hydrogens from carbons 1 and 4 would be sterically inhibited due to resonance forms violating Bredt's rule (XXXV). Another factor which would destabilize a cationic center at C-7 is the increase in angle strain in going from sp^3 to sp^2 hybridization.



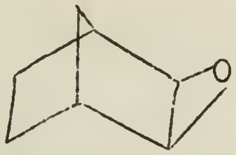
XXXV

In the free-radical monochlorination of norbornane (15) it has been observed that very little if any of the 7-isomer is formed. The percentage of 7-norbornyl chloride varied from 0 to 5, the main products being the *exo*-2- and *endo*-2-norbornyl chlorides. Possible explanations for the lower reactivity at the 7-position are similar to the cationic example in that angle strain might be increased in going to the 7-norbornyl radical and also any hyperconjugative resonance stabilization would be lost. The only chlorinations which gave the 7-isomer were those which involved the highly reactive and therefore unselective chlorine atom. Thus the chlorination involving the trichloromethyl radical gave no 7-isomer.

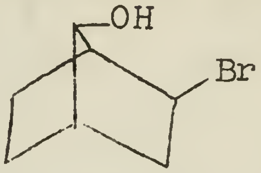
In 1957 Winstein and co-workers communicated the synthesis and novel solvolysis product of the previously unavailable *syn*-7-norbornenyl tosylate (XXXVI) (16). When bicycloheptene oxide (XXXVII) was opened with hydrobromic acid a bromohydrin (XXXVII) was obtained as a result of a Wagner-Meerwin rearrangement. The action of potassium *t*-butoxide in benzene on the tosylate of XXXVIII yielded *syn*-7-norbornenyl tosylate in about 80% yield.



XXXVI

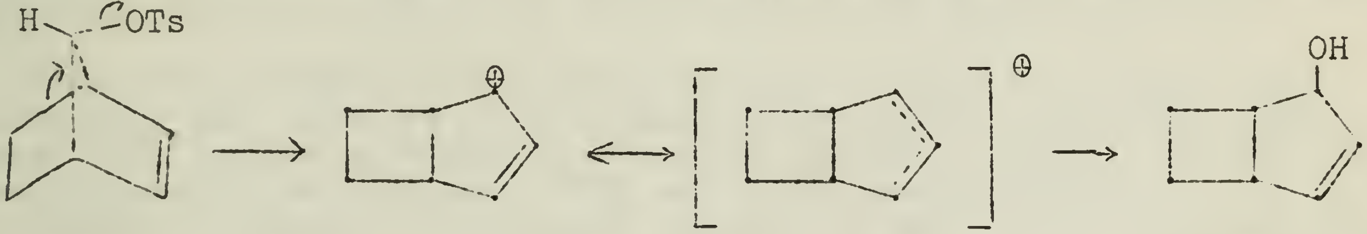


XXXVII



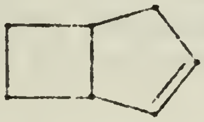
XXXVIII

The first-order rate constant of acetolysis was found to be 2.6×10^{-11} sec^{-1} at 25°. Although this is slower than the *anti*-isomer by a factor of 10^7, nevertheless anchimeric assistance is still evident from the nature of the product (XXXIX). Assistance in this case however is from the C-6 methylene rather than the C-2, C-3 double bond which was true for the *anti*-isomer.



XXXIX

The unknown alcohol was obtained in about 90% yield by hydrolysis of *syn*-7-norbornenyl tosylate with aqueous 0.2 *N* $NaHCO_3$ at 100°. This unsaturated alcohol was found to be different from all the known norbornenols by comparison of the infrared spectra. When bicyclo-[3.2.0]heptene-2 (XL), the parent hydrocarbon of the suspected alcohol, was oxidized with SeO_2 in acetic anhydride an unsaturated alcohol was obtained which proved to be identical with the unknown.



XL

Some related work has been done on 7-camphenyl derivatives by van Tamelen and his co-workers (17). These derivatives were prepared from camphenamine, which was shown to be *anti*-7-aminocamphene (XLI) in earlier work (18). Such a system was a convenient possibility for study of the 7-camphenyl carbonium ion.

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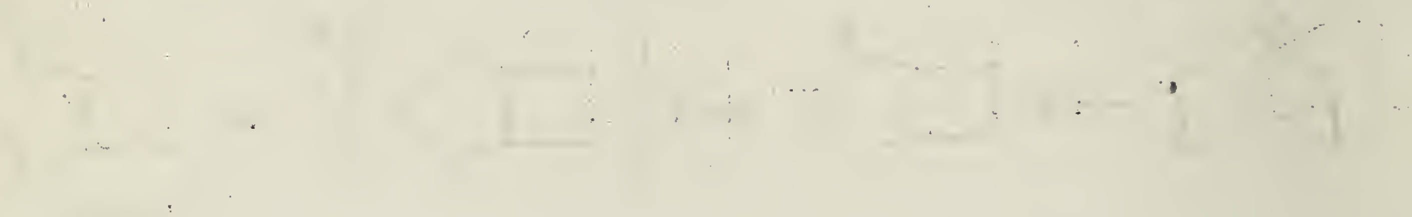

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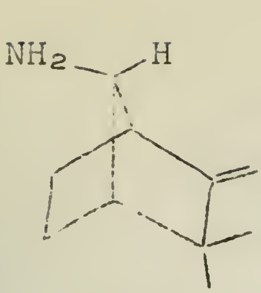
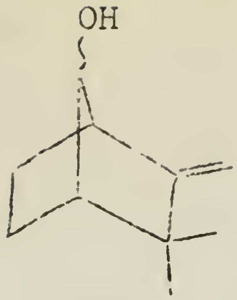
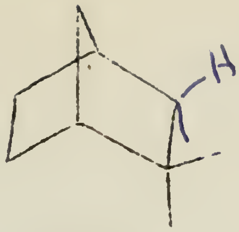


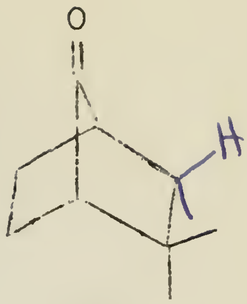
XLI



XLII



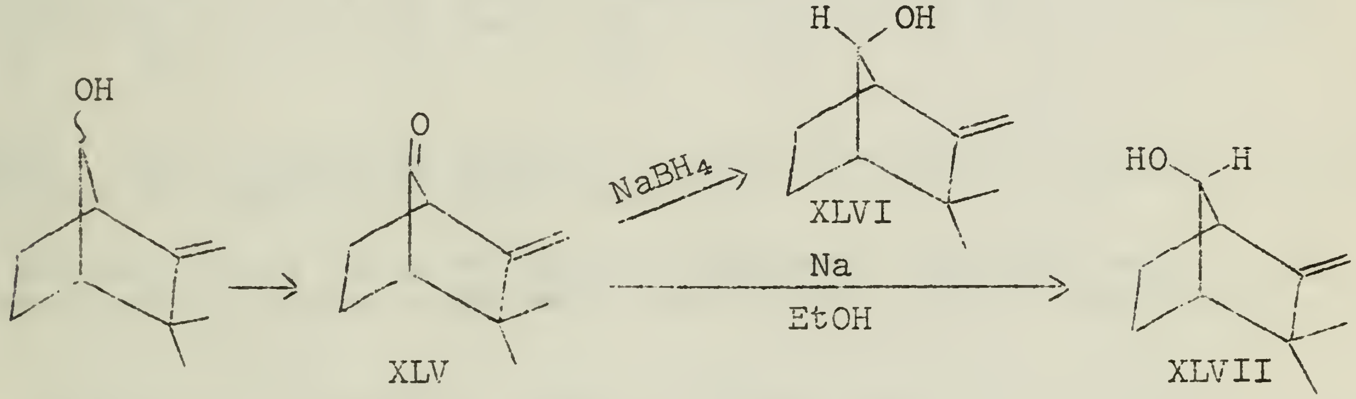
XLIII



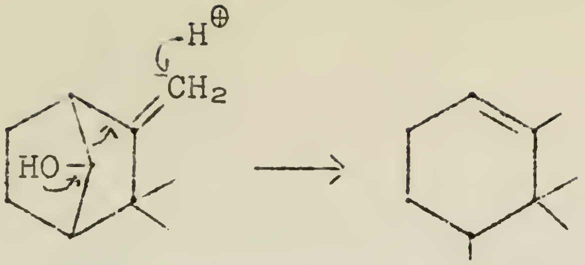
XLIV

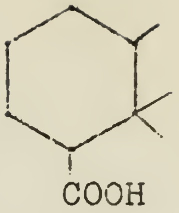
Diazotization of XLI yielded a solid alcohol designated as β-isocamphor (XLII) and shown to have the same skeletal structure as camphenamine by its complete reduction to the known hydrocarbon, isocamphane (XLIII). This was accomplished by catalytic reduction followed by oxidation to the saturated ketone XLIV and its reduction by desulfurization of the ethylenethioketal with Raney nickel. It was shown that the ketone XLIV did not suffer any exchange of hydrogen on treatment with sodium deuteroxide in O-monodeuterioethanol. This fits the proposed structure since proton removal at C-1 or C-4 is prevented by the geometrical constraints imposed by the bridged structure.

The configuration at C-7 was determined in the following manner. β-Isocamphor was oxidized to the unsaturated ketone XLV, which when reduced with sodium borohydride and also sodium in ethanol yielded two isomeric unsaturated alcohols XLVI and XLVII respectively. As it is well known that hydride reductions involve an approach of the reducing species from the least hindered side and that sodium in ethanol gives the more stable isomer, the above assignments could be made. β-Isocamphor proved identical with structure XLVII with the anti-configuration.



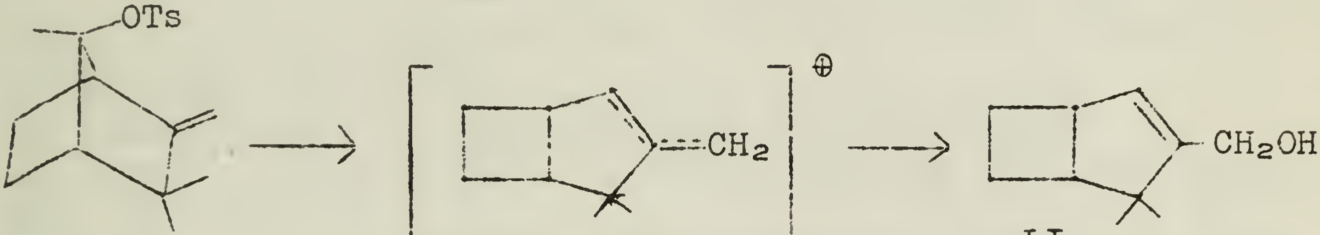
In an attempt to generate a carbonium ion at the 7-position of the camphene system, β-isocamphor was treated with aqueous alcoholic sulfuric acid for several days. The product which was isolated proved to be an aldehyde by its infrared absorption and oxidation with alkaline silver oxide to an optically inactive acid. A possible accounting for these products is shown in XLVIII. The proposed structure for the unknown aldehyde XLIX was proven by oxidation to the acid followed by hydrogenation to give the known saturated acid L. The double bond as assigned in XLIX is the only possibility that was compatible with the NMR spectra of the unsaturated acid which showed an olefinic hydrogen peak equal in intensity to the carboxylic hydrogen peak.





XLVIII XLIX L

The possibility of generating the 7-camphonyl carbonium ion by solvolysis of the 7-camphenyl tosylates was also investigated. Acetolysis of the tosylate of β-isocamphor XLVII yielded a product presumed to be the unrearranged acetate since hydrolysis of this product gave back β-isocamphor. The tosylate of syn-camphenol XLVI behaved quite differently on hydrolysis in aqueous bicarbonate at 200°, giving a product which corresponded to neither 7-camphenol and showing no infrared bands characteristic of a terminal methylene grouping. Manganese dioxide oxidation, considered to be specific for allyl alcohols, converted the product to an α,β-unsaturated carbonyl derivative. This evidence suggested structure LI for the unknown alcohol. This product is similar to that obtained by Winstein in the solvolysis of syn-7-norbornenyl tosylate.



LI

The acetolysis rates of various camphenyl tosylates were measured and are given in Table V. The values for the unsaturated esters are quite unexpected in that both are less than that of the camphanyl tosylate despite the fact that anchimeric assistance can be had from the exocyclic double bond. This should result in a non-classical carbonium ion LII very comparable to the cholesteryl carbocation LIII formation of which is associated with a rate increase of about 10^2 over cyclohexyl tosylate. From this it is clear that the

Table V. Acetolysis Rates of Some Tosylates at 140°

Tosylate	rel. k
anti-7-Camphenyl	6
syn-7-Camphenyl	13
syn-7-Isocamphanyl	18
7-Norbornyl	1

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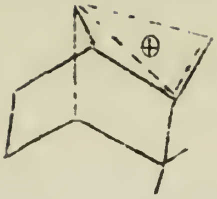
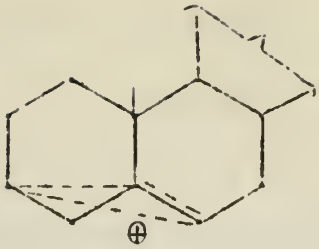


LII



LIII

7-camphenyl homoallylic carbonium ion (LII) does not enjoy the same degree of stability as the cholesteryl cation LIII.

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KINETIC STUDIES WITH NUCLEAR MAGNETIC RESONANCE

Reported by T. K. Dykstra March 2, 1959

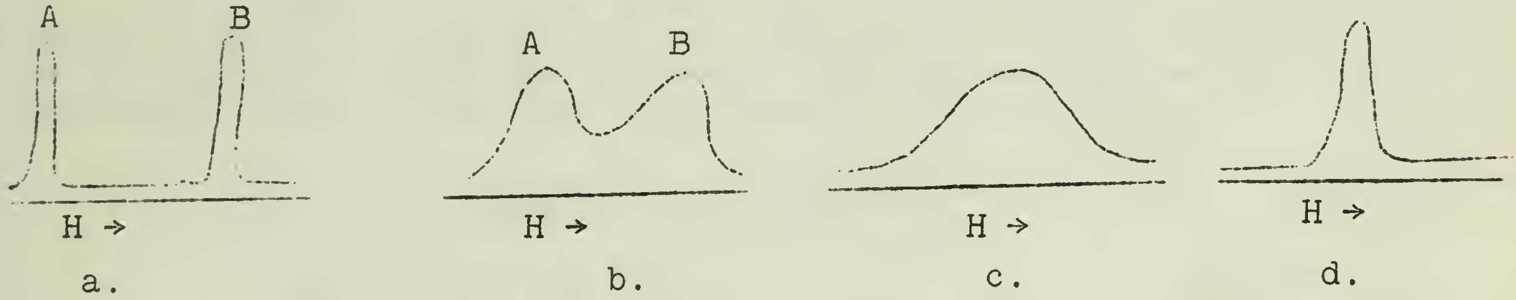
INTRODUCTION

Within the last few years work has been done to develop the use of nuclear magnetic resonance as a tool to study the kinetics of reactions proceeding too fast to be measured by conventional methods. Kinetic studies with NMR have centered about reactions in which the electronic environment of a hydrogen atom, or some other atom whose nuclear spin is one-half, is rapidly changed. This rapid change in electronic environment may take place in a variety of ways, such as exchange of the nuclei observed between compounds, exchange of electrons between compounds containing the nuclei observed, rotation about a single bond, and inversion of pyramidal nitrogen compounds.

It is the purpose of this seminar to describe briefly the relationship between reaction rates and the shape of the NMR spectrum and to discuss a few representative examples of quantitative kinetic studies employing the NMR method. If a review of the principles of NMR is desired, good sources are available (1,2,3).

THEORETICAL CONSIDERATIONS

A qualitative and simplified picture illustrating the relationship between the rate of change of electronic environment and the shape of an NMR line might be presented as follows (4). Consider two protons at sites A and B, and assume that these sites exert different local magnetic fields on the proton. In the absence of proton exchange between sites, or in the region of very slow exchange, each proton resonance will appear at the position corresponding to the applied magnetic field needed to produce resonance between the nuclear magnetic dipole precessing about the magnetic field axis and the radiofrequency field rotating perpendicularly to the magnetic field axis. This situation is represented in Figure 1a. In the event of proton exchange between sites A and B, the energy of the proton is perturbed by a change in energy which is time dependent. As the time during which a proton is in a given energy state decreases (*i. e.*, as the exchange rate increases), our knowledge of the energy of the proton at a given instant decreases according to the uncertainty principle. This increased uncertainty of the energy shows up as an increase in the line width of the spectrum as in Ib. As the exchange rate increases further, the change in the energy of the proton becomes too rapid for one to detect whether the proton is at the energy level corresponding to site A or at that energy corresponding to site B.



Thus there appears a single peak, corresponding to an average perturbation, which is situated midway between the proton signals observable in the absence of exchange (Figure Ic). In the region of extremely fast exchange, the precessing nuclear moments are not in any one frequency state long enough to progress out of phase from the frequency corresponding to an average energy state and the single resonance line narrows (Id). The narrowing of this single line is limited, of course, by those factors which control line width such as inhomogeneity of the magnetic field.

Gutowsky and coworkers (5,6), starting from the equations of Bloch (7) which describe nuclear magnetic resonance line shapes, have derived equations which relate the average lifetime of a nucleus (spin = 1/2) in a given electronic environment to the observed separation between resonance lines ($\delta\omega_e$), the separation between lines in the absence of exchange ($\delta\omega$), and the spin-spin relaxation time, T_2, which might be termed the "phase memory time" (8). That is, if two nuclei are precessing in phase with each other at time $t = 0$, then the probability of their precessing in phase at some other time, t, is: e^{-t/T_2}. The above model involving two sites is used assuming it to involve a liquid in which there is negligible dipolar broadening of a resonance line. The two lines resulting from the absence of exchange will be separated by a frequency difference of $\delta\omega$. The relative intensities of these lines will be proportional to the proton fractions, p_A and p_B, contributing to the line. Labeling the protons at A as N_A^* and those at B as N_B^*, then at a given instant, $\frac{dN_A^*}{dt} = -k_A N_A^*$ and $\frac{dN_B^*}{dt} = -k_B N_B$, where $k_A p_A = k_B p_B$. The specific rate constants are reciprocals of the average lifetimes at a site, τ_i. Therefore, $k_A = \frac{1}{\tau_A} = \frac{p_B}{\tau}$ and $k_B = \frac{1}{\tau_B} = \frac{p_A}{\tau}$ where $\tau = \frac{\tau_A \tau_B}{\tau_A + \tau_B}$. Equations were obtained for the case when $p_A = p_B$ (adjustable by varying mole fractions of the mixture components) and $\tau_A = \tau_B = 2\tau$.

If the line widths are small compared with the line separation in the absence of exchange (i. e., if $T_2\,\delta\omega$ is large), then the overlap of components does not influence the observed separation, and a relatively simple equation, independent of T_2, is obtained.

$$\delta\omega_e = \left(1 - \frac{2}{\tau^2 \delta\omega^2}\right)^{1/2} \text{ if } \tau\delta\omega > \sqrt{2} \qquad \text{Eq. I}$$

$$\delta\omega_e = 0 \text{ if } \tau \leq \sqrt{2}$$

If overlap effects are taken into consideration, the expression is somewhat more complex, as shown by Equation II.

$$\delta\omega_e = \pm 2 \left\{ -s\left(\frac{1}{\tau} + \frac{T_2}{\tau^2}\right) \pm s^{1/2} \left(\frac{\delta\omega}{2}\right) \left(\frac{T_2^2}{\tau^3} + \frac{4T_2}{\tau^2} + \frac{4}{\tau}\right)^{1/2} \right\}^{1/2} \qquad \text{Eq. II}$$

$$\text{where } s = \left[\frac{1}{T_2} + \frac{\tau}{T_2^2} + \tau\left(\frac{\delta\omega}{2}\right)^2\right]$$

From equations I and II it is possible to compute the dependence

of $\delta\omega_e$ on τ and T_2. The quantity $\delta\omega$ can be measured experimentally. Bloembergen, Purcell and Pound (9) have stated that in the absence of exchange effects and overlap effects, the line width at half maximum intensity in cycles per second is equal to $\frac{1}{\pi T_2}$. This experimental T_2 includes all contributions to line broadening and thus introduces some error. Figure IIa shows the dependence of $\delta\omega_e$ on τ for various values of $T_2\delta\omega$. It is obvious from IIa that for values of $T_2\delta\omega$ less than 3.5, $\delta\omega_{e,\tau\to\infty} \neq \delta\omega$. Thus it is seen that overlap of the resonance lines decreases their apparent separation. To correct for this, a true limiting separation ($\delta\omega$) can be obtained by substituting the observed separation corresponding to $\tau \to \infty$, ($\delta\omega_\infty$), into equation II. The value of the true limiting separation ($\delta\omega$) is read from a graph of $\delta\omega/\delta\omega_\infty$ as a function of $\frac{2}{T_2\delta\omega_\infty}$ (Figure IIb). To determine τ, the values of T_2, $\delta\omega$, and $\delta\omega_e$ are applied to the graph in Figure IIa. The graph in Figure IIc provides a better means of interpolating the quantity $\frac{1}{T_2\delta\omega}$ and thus provides greater accuracy for the measurement of τ.

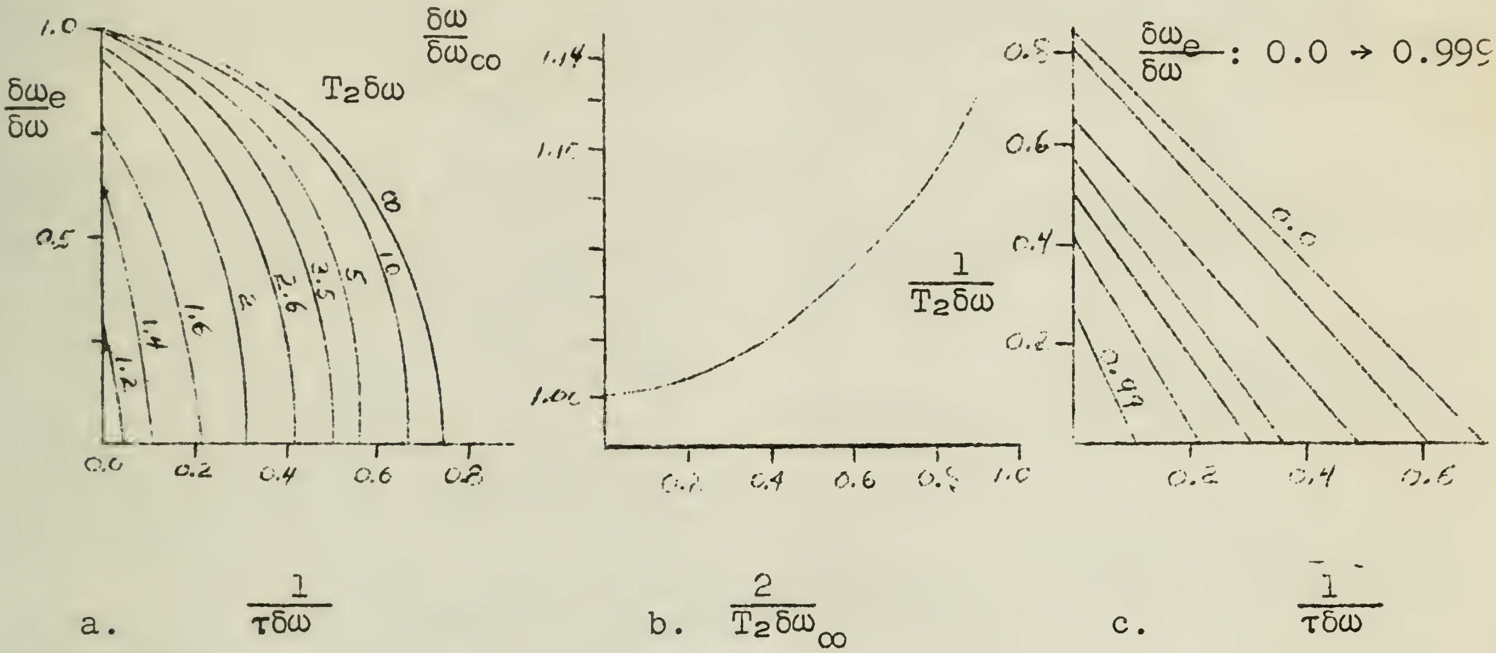


Figure II

In the treatment given above it is assumed that T_2 is not influenced by the exchange rate, which may or may not be true depending on the particular system and the experimental conditions.

McConnell (10) has also treated the above model and has extended the treatment to other systems. Kaplan (11) has generalized the treatment over that given above. However, most studies involving organic molecules make use of the type of analysis described in this seminar.

SOME KINETIC STUDIES INVOLVING ORGANIC MOLECULES.

1. Rotation about the carbon-nitrogen bond of some substituted amides.

Pauling (12) postulated that the structure involving a double bond between carbon and nitrogen is significant in the consideration of the electronic structure of amides (Figure III). Gutowsky and Holm (6) have applied their theoretical analysis to a study of rotation about the C-N bond in various substituted formamides and acetamides.

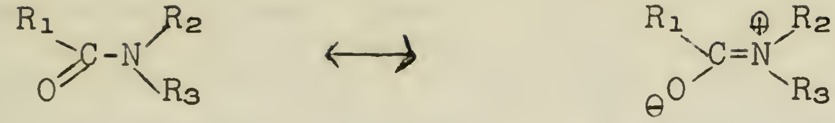


Figure III

The spectra of various amides are shown schematically in Figure IV. The spectra were recorded at 29°. The radiofrequency was fixed at 17.735 Mc with $\delta = \left(\frac{H_{H_2O}-H_{amide}}{H_{H_2O}}\right)10^5$, with water as the reference. The assignments were made on the basis of relative intensities and known chemical shift values (13). The spectrum of N,N-dimethylformamide (DMF) shows a doublet due to the nonequivalence of the N-methyl groups with respect to the carbonyl group. It was concluded that this doublet is due to chemical shift and not to electronic coupling between the carbonyl proton and N-methyl protons, on the basis of three facts: 1) the $H\text{-}\overset{\overset{O}{\|}}{C}\text{-}$ proton is not a multiplet; 2) N,N-dimethylacetamide (DMA), where the carbonyl hydrogen is replaced by a methyl group, also gives a doublet for the N-methyl protons and not a quartet; 3) the separation of the doublet was proportional to the applied magnetic field. Thus evidence for the existence of a partial double bond is supported. The doublets of both DMA and DMF approach one another as the temperature is increased until coalescence of the doublets occurs at temperature T_c, thus indicating an increase of the rotation rate with temperature.

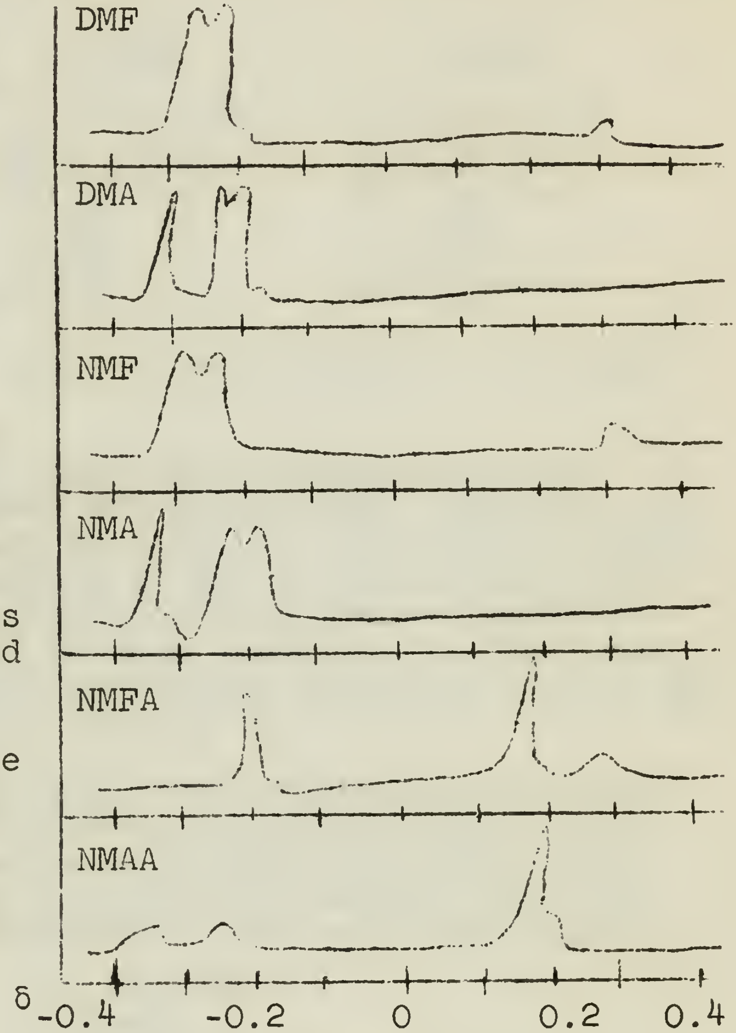


Figure IV

The equations and graphs corresponding to appreciable overlap of resonance signals in the absence of exchange were applied. It was assumed that changing temperature had little effect on T_2, since the main contribution to line width was considered to be the inhomogeneity of the magnetic field. The results of the experiments are summarized in Table 1, which is abbreviated.

Table 1

DMF			DMA		
T, °K	$\delta\omega_e$ (rad.sec^{-1})	$\frac{1}{\tau\delta\omega}$ rad^{-1}	T, °K	$\delta\omega_e$ (rad.sec^{-1})	$\frac{1}{\tau\delta\omega}$ rad^{-1}
236	20.1 ± 0.3	0.00 ± 0.03	249	24.4 ± 0.9	0.00 ± 0.1
325	18.5 ± 1.2	0.11 ± 0.04	307	21.9 ± 1.1	0.19 ± 0.07
347	16.6 ± 1.2	0.20 ± 0.03	313	20.4 ± 0.9	0.25 ± 0.04
362.5	13.2 ± 0.3	0.30 ± 0.01	319.7	15.4 ± 0.9	0.39 ± 0.03
369	11.9 ± 0.6	0.33 ± 0.01	322.5	9.8 ± 0.7	0.48 ± 0.01

If rotation about the carbon-nitrogen bond is considered to be a typical rate process, then $k = v_o \exp(-E_a/RT)$, where E_a is the activation energy of the process, and v_o is the frequency factor. Since $k = \frac{1}{2\tau}$, then $\log\left(\frac{1}{\tau\delta\omega}\right) = \log\left(\frac{2v_o}{\delta\omega}\right) - \frac{E_a}{2.3\ RT}$. A plot of $\log\left(\frac{1}{\tau\delta\omega}\right)$ versus $\frac{1}{T}$ provides a straight line whose intercept and slope afford a calculation of v_o and E_a respectively. The results are summarized for DMF and DMA in Table 2. The errors in these quantities are apt to be quite large since the error encountered in measuring small $\delta\omega$'s and line widths is quite large.

Table 2

	DMF	DMA
T_2, sec. rad.$^{-1}$	0.14 ± 0.03	0.18 ± 0.04
$\delta\omega_\infty$	20.1 ± 0.3	24.4 ± 0.9
$\delta\omega$	20.4 ± 0.3	24.6 ± 1.1
T_c, °K	372	325
E_a, Kcal.	7 ± 3	12 ± 2
v_o, sec.$^{-1}$	10^3-10^7	10^7-10^{10}

Larger magnetic fields would tend to improve the accuracy, all other things being equal.

The spectra of N-methylformamide (NMF) and N-methylacetamide (NMA) are superficially similar to those of DMF and DMA. However, the N-methyl doublet does not widen with an increase of the magnetic field strength, thus indicating that the doublet is due to spin-spin interaction between the N-methyl and >N-H protons via indirect electronic coupling (14). The >N-H signal itself is very broad due to the above interaction which results in a quartet, quadrupole interaction with the nitrogen nucleus, and possible hydrogen bonding.

The spectra of N-methylformanilide (NMFA) and N-methylacetanilide (NMAA) are similar to those of DMA and DMF except that no multiplets are present. This is attributable to the fact that the phenyl ring competes with the oxygen of the carbonyl group for electrons as seen in Figure V. Thus the double bond character of the carbon-nitrogen bond is decreased, and the rate of rotation about this bond is increased.

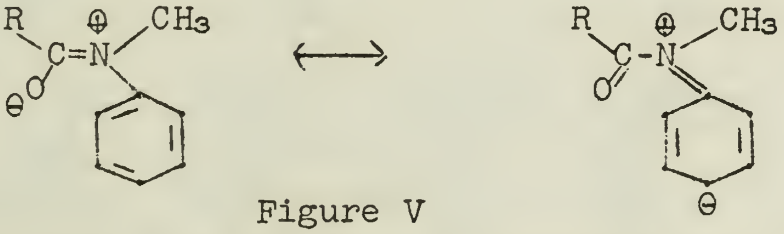


Figure V

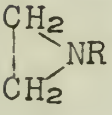
2. The inversion rates of some substituted ethylenimines.

Kincaid and Henriques (15) estimated the energy of activation for the inversion of N-methylethylenimine to be approximately 25 kcal. per mole. Assuming resolution to be impossible unless $k_{inversion}$ is less than 10^{-5} sec.$^{-1}$ at room temperature, they calculated from the Arrhenius equation, using a frequency factor of 10^{13}, that the activation energy would have to be above 25 kcal. per mole to meet the requirement. As yet, chemical resolution of substituted ethylenimines (aziridines) has not been achieved.

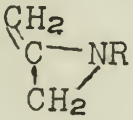
Bottini and Roberts (16) have applied the equations of Gutowsky and his coworkers to a study of the kinetics of the inversion of various substituted aziridines. The NMR spectra were recorded at various temperatures with a fixed radiofrequency field of 40 Mc. The assignment of the ring substituents was based on work reported by Roberts and Bottini previously (17), and in this paper. The positions of the resonance lines were expressed in p.p.m. relative to the benzene resonance at 25-35°.

The NMR spectrum of 1-ethylaziridine at 30° contains two triplets (δ = 5.60 and 6.28) which are best interpreted as being due to pairs of nonequivalent ring hydrogens, one pair being cis to the N-ethyl group, and the other pair trans to the N-ethyl group. The triplet is, of course, due to mutual spin-spin splitting. As the temperature of the sample is increased, these two triplets overlap and eventually coalesce at approximately 108° C. This coalescence can be accounted for by postulating that as the temperature is increased, the rate of inversion about the nitrogen atom increases until at T_c ($\sim$108°) the inversion is taking place too fast for the radiofrequency field to determine whether a given pair of hydrogen atoms is cis or trans to the N-ethyl group. In contrast to this, 1-ethyl-2-methylene-aziridine shows only a single absorption line ($\delta \simeq 5.20$) for the ring methylene protons at 30°. If the temperature is lowered, however, this single line is split into two components divided by 30 c.p.s. at and below -77° C. This separation into two components corresponds to a rate of inversion low enough to give the hydrogens of the ring methylene groups identity with respect to the N-ethyl group. Obviously, then, the rate of inversion through the nitrogen atom of the aziridines depends in part on the various substituents present. For a number of substituted aziridines, Roberts and Bottini (16) have calculated τ', the average lifetime of a given molecule before inversion occurs, and k', the specific rate constant of inversion. Their results are given in Table 3.

Table 3



I



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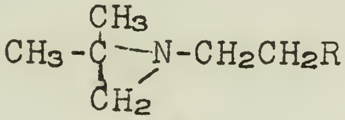
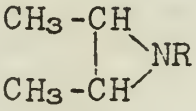
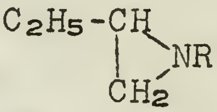


III



IV



V

Compound	R	T_c, °C	τ', sec^{-1}	k', sec^{-1}	Remarks
Ib	C_2H_5	108 ± 5	0.017	60	
Ib	C_2H_5	> 145	> 0.017	< 60	in D_2O
Ic	$CH_2C_6H_5$	105 ± 5	0.017	60	
Id	$CH_2CH_2C_6H_5$	96 ± 5	.014	69	
Ie	C_6H_{11}	95 ± 10	.020	51	
If	t-C_4H_9	< -77	-	-	pure and in 0.01 N-methanolic NaOH
Ig	C_6H_5	< -77	-	-	pure and in toluene
Ig	C_6H_5	-60 ± 10	.024	42	
II	C_2H_5	-65 ~~103~~ ± 10	.015	67	
II	C_2H_5	-25 ~~105~~ ± 10	.015	67	in 0.01 N methanolic NaOH
IIIa	CH_2OH	55 ± 5	.11	8.9	gem dimethyls measured
IIIb	$CO_2C_2H_5$	55 ± 5	.075	13	gem dimethyls measured
IV cis	C_2H_5	140	-	-	spectrum unchanged up to 140°
IV trans	C_2H_5	58	.064(?)	16(?)	gem dimethyls measured
V	C_2H_5	140	-	-	spectrum unchanged up to 140°.

The authors did not calculate the energies of activation for inversion from the equation: $k' = K(\frac{kT}{h})e^{-\Delta E/RT}$ due to uncertainty concerning the correct value of K.

Analysis of the results in Table 3 reveals many items of interest. First of all, conjugation with nitrogen must have one of two effects. Either it produces essentially planar molecules with equivalent ring and substituent hydrogens, or it greatly increases the inversion rate. The experiment with 1-ethyl-2-methylene-aziridine described previously prompts one to choose the latter effect. Electrons could be delocalized from the methylene double bond, causing the structure shown in Figure VI to contribute to the electronic structure. This delocalization would greatly aid the attainment of a planar inversion transition state. 2,4,6-Tris-(1-aziridinyl)- -triazine (VII) was prepared. The NMR spectrum gave no evidence of resonance separation at -40° C. and -10° C., the crystallization points in chloroform and water respectively.

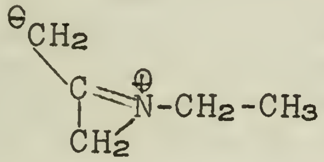


Figure VI

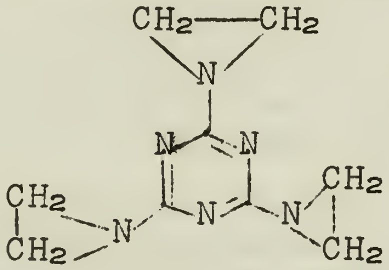


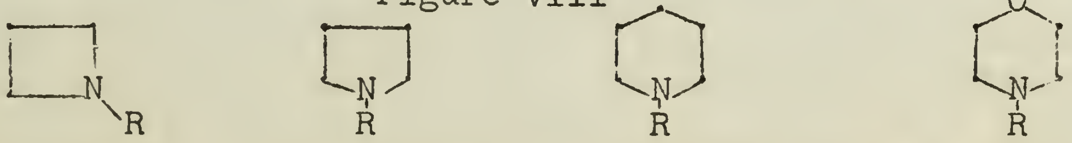
Figure VII

The effect of bulky substituents can be seen. From the facts that the inversion rates of Ic and Id in Table 3 are only slightly greater than that of Ib, one could conclude that steric effects are much greater than weight effects on the inversion rate. The largest bulk effect should be present in 1-*t*-butyl-aziridine in which an examination of the models suggests that steric interaction must be present between the ring and methyl hydrogens if pyramidal geometry is to be maintained. If electronic effects are equal in the ground state and the transition state, then lowering of the energy barrier must be due to hydrogen-hydrogen repulsion in the ground state. Steric effects also probably increase the inversion rates of III and IV *trans*. The compounds IV *cis* and V very likely preferentially have the ring substituents *trans* to the 1-ethyl-group. Thus, no appreciable change takes place in the spectrum up to 140°.

Some of the inversion rates were decreased when the sample was placed in a hydroxylic solvent. This effect is presumably due to stabilization of the ground state through hydrogen bonding. Thus the two ring hydrogen signals of 1-ethyl-aziridine in D_2O did not coalesce even at 145°, while in the pure liquid coalescence occurred at approximately 108°. This effect is also evident in the cases of 1-ethyl-2-methylene-aziridine and 1-phenylaziridine.

The NMR spectra of various derivatives of azetidine, pyrrolidine, piperidine and morpholine (Figure VIII) showed that at -77°, the inversion of these compounds was too rapid to measure.

Figure VIII



azetidine pyrrolidine piperidine morpholine

3. Studies involving proton exchange between different chemical sites.

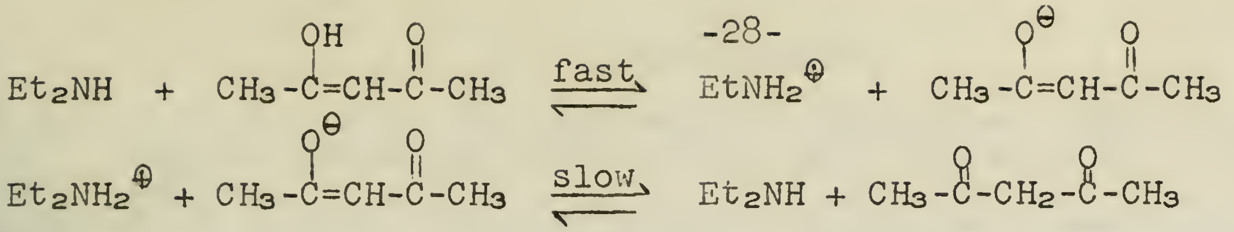
Schneider and Reeves (18) have studied the kinetics of systems in which proton exchange of the following type takes place: X-H---Y $\rightleftharpoons$ X----H-Y. As the rate of exchange of the proton between the different sites X and Y via the hydrogen bond increases, the two separate resonance lines will broaden and eventually coalesce.

The authors observed the NMR spectrum of a 2:1 molar ratio mixture of ethanol to water (thus adjusting p_{EtOH} to equal p_{H_2O}) at various temperatures. Assignments were made on the basis of relative intensities and work done by Weinberg and Zimmerman (19) who observed the spectrum of H_2O-ethanol mixtures at various H_2O-ethanol ratios. At room temperature (27°) the spectrum contained two singlet OH peaks separated by approximately 30 c.p.s. with the H_2O proton resonance occurring at the higher field. By increasing the temperature, coalescence of the peaks occurred at 72°. Applying the equations of Gutowsky and his coworkers, the value of τ', the lifetime of the proton at a given site, was calculated to be 7.3×10^{-3} sec. at 72°. Computing τ' at various temperatures, the authors calculated the energy of activation for the exchange to be 7.5 ± 0.5 kcal. per mole.

Studies were also made by Schneider and Reeves (18) of the proton exchange involved in the base-catalyzed enolization of acetylacetone. The NMR spectrum of pure acetylacetone at room temperature was observed. The assignment of groups based on work by Shoolery and coworkers (20), Bhar (21) and Reeves (22) are given in Table 4. The chemical shifts are given in p.p.m. relative to the enol methyl signal. The spectrum of the 1:1 addition complex (m. p. 41.5°) of diethylamine and acetylacetone was observed at 45°. The assignments, with chemical shifts again relative to the enol methyl in p.p.m., are given in Table 4. Due to the combined peak for $>$NH, enol -OH and enol =CH-, it was concluded that fast proton exchange is taking place between these sites. In an effort to analyze the broad coalesced signal further, the spectrum of the complex dissolved in CCl_4 to a concentration of 15 mole percent was observed. At 27°, what had been a broad single band now existed as two bands with an intensity ratio of 2:1. The band with the relative intensity of 2 was at -5.66 p.p.m. (relative to enolic methyl) and was dependent in intensity on the amine concentration. No mention of the position dependence of this line on amine concentration was made. The other band occurred at -3.43 p.p.m. At 74° these two bands coalesced to a single sharp peak at -3.73 p.p.m. These observations can be interpreted with aid of the equations in Figure IX. The peak with a relative intensity of 2 might represent protons exchanging rapidly as in equation (a). The exchange of protons between the amine and enol =CH- group is slower and thus at 27°, a peak with a relative intensity of 1 appears. As the temperature is raised, however,

Table 4

Pure acetylacetone		1:1 diethylamine-acetylacetone	
Group	Chem. Shift	Group	Chem. Shift
enol $-CH_3$	0	amine $-CH_3$	+ 0.92
keto $-CH_3$	-0.17	enol $-CH_3$	0
keto $-CH_2-$	-1.65	amine $-CH_2-$	- 0.68
enol =CH-	-3.58	$>$NH enol -OH enol =CH-	- 4.60(broad)
enol -OH	-13.58		



$$Et_2NH + CH_3-\overset{OH}{\overset{|}{C}}=CH-\overset{O}{\overset{\|}{C}}-CH_3 \overset{fast}{\rightleftharpoons} EtNH_2^{\oplus} + CH_3-\overset{O^{\ominus}}{\overset{|}{C}}=CH-\overset{O}{\overset{\|}{C}}-CH_3 \qquad (a)$$

$$Et_2NH_2^{\oplus} + CH_3-\overset{O^{\ominus}}{\overset{|}{C}}=CH-\overset{O}{\overset{\|}{C}}-CH_3 \overset{slow}{\rightleftharpoons} Et_2NH + CH_3-\overset{O}{\overset{\|}{C}}-CH_2-\overset{O}{\overset{\|}{C}}-CH_3 \qquad (b)$$

Figure IX

this rate also increases to a point where the =CH- proton's environment is also averaged and a single peak appears for all three protons.

4. Measurement of electron exchange rates with NMR.

Bruce, Harberg, and Weissman (23) have studied with NMR an example of electron exchange proceeding too slowly to be studied with electronic paramagnetic resonance. The NMR spectrum of N,N,N',N'-tetramethyl-p-phenylenediamine (TMPD) at 6420 gauss in D_2O (pH = 3.2) consists of two lines which are attributable to the ring and methyl protons. When Wurster's Blue (WB), the one-electron oxidation product of TMPD is added to the system, the TMPD lines broaden linearly with the concentration of WB. If water and acetate ion are added to the system, their resonance lines are unaffected by the addition of WB. These facts indicate an exchange of electrons between TMPD and WB which is first-order in WB. The reaction is shown in Figure X. The reaction rate constant in this type of system is given by: $k = \frac{\pi \Delta V}{\sqrt{3}\,A}$ where A is the molar concentration of the paramagnetic species (WB) and ΔV is the full line width in frequency at half-maximum intensity assuming a Lorentzian line shape. The reaction rate constant for the above exchange was calculated to be: $k = 2.5 \times 10^4$ liter $mole^{-1}$ $sec.^{-1}$.

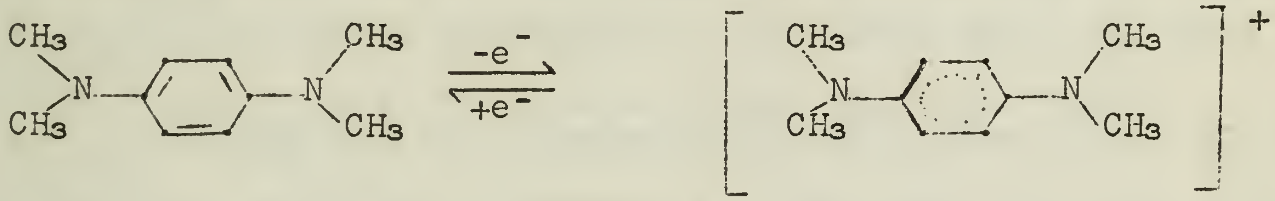


Figure X

5. Other studies.

The above discussion includes only a few of the kinetic studies made using the NMR method. There are other quantitative studies to which only brief reference will be made. Meiboom, Grunwald and coworkers have studied the protolysis kinetics of N-methylacetamide (24) and methylamine (25) using calculations based to a certain extent on the analysis of Gutowsky and coworkers presented in this seminar. Looney, Phillips and Reilly (26) have done quantitative work on the kinetics of hindered rotation about the nitrogen-nitrogen bond of various nitrosamines. Meiboom, Luz, and Gill (27) have studied the rates of proton exchange between H_2O and ethanol as a function of pH.

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STEREOCHEMISTRY OF REACTIONS AT PRIMARY CARBON ATOMS

Reported by D. H. Dybvig March 9, 1959

INTRODUCTION

Knowledge of the stereochemical course of many reactions has proven to be valuable in determining their mechanisms. In the case of monofunctional aliphatic systems the mechanistic course of a given reaction may be quite dependent on the stereochemistry of the system, as exemplified by the various types of displacement reactions. Since the functional group under investigation must be situated at an asymmetric carbon atom there has been extensive use of secondary carbinols and their simple derivatives.

Ordinary primary compounds do not lend themselves to stereochemical means of study. In recent years, however, substitution of a hydrogen atom by a deuterium atom has rendered primary carbon atoms asymmetric and potentially optically active. Fickett (1) has shown theoretically that such hydrogen-deuterium asymmetry can appreciably affect optical activity, and previously this fact had been shown experimentally by the synthesis of ethylbenzene-α-d (2), menthane-3-d, and menthane-2,3-d_2 (3,4).

Of the several possible approaches to the preparation of an optically active primary carbon atom bearing deuterium, the stereospecific chemical and biological reductions of aldehydes have proven satisfactory.

SYNTHESIS OF 1-BUTANOL-1-d BY CHEMICAL REDUCTION

Doering and Young have shown the Meerwein-Pondorf reduction to be partially stereospecific (5). For example, the reaction of 6-methylheptanone-2 with optically pure aluminum 2-butoxide produces 6-methylheptanol-2 of 6% optical purity. An adaptation of a method which is probably mechanistically similar to the Meerwein-Pondorf reaction, the reduction of ketones with alkoxymagnesium halides (6), was used by Streitwieser in the reduction of aldehydes (7).

Streitwieser obtained (+)-2-octanol-2-d in near optical purity by the reduction of methyl hexyl ketone with lithium aluminum deuteride followed by resolution of the racemic mixture using classical methods. (+)-2-Octanol-2-d was treated with an equivalent amount of ethylmagnesium bromide, in order to prepare the stereospecific reducing agent, 2-octyl-2-d-oxymagnesium bromide, and was allowed to stand with an equimolar quantity of butyraldehyde in ether solution for three days. (-)-1-Butanol-1-d having a small but definite rotation, $[\alpha]^{25}D$ $-0.032 \pm 0.002^{\circ}$ (neat), was obtained in fair yield. The identity of the product was established by comparison of physical constants and infrared spectrum with those of 1-butanol-1-d prepared unequivocally by reduction of butyraldehyde with lithium aluminum deuteride.

In order to demonstrate conclusively that the small rotation obtained was indeed a property of the 1-butanol-1-d isolated and not due to an optically active impurity, several control experiments were run. Using the same reaction conditions, non-deuterated reactants produced butanol with no detectable optical activity. In several experiments using slightly different conditions consistent yields

(24-29%) of 1-butanol-1-d having comparable optical activity were obtained. Distillation was used as a means of purification, and it was found that after two distillations the magnitude of optical rotation did not vary. The chemical purity of optically active 1-butanol-1-d was demonstrated by the constancy of rotation of its hydrogen phthalate ester during repeated recrystallization and by its regeneration from this ester with unchanged rotation (8).

The final demonstration of optical activity as a unique property involved the comparison of the rate of a reaction at the asymmetric center as followed by the change in optical rotatory power and the rate as followed by a non-stereochemical method. The equality of the rate of displacement of 2-iodoöctane by iodide ion in acetone as followed by the racemization of the optically active haloalkane with the rate as followed by the gain of radioactivity using radioactive iodide ion, was one of the early facts supporting displacement accompanied by inversion (9). Streitwieser, making the justifiable assumption that the same hypothesis is true also for primary halides, has shown that the rate of racemization of 1-bromobutane-1-d with lithium bromide is equivalent to the rate of radioactive exchange with lithium radiobromide. The second-order rate constant for displacement of n-butyl bromide with lithium radiobromide in 90% aqueous acetone at 25° is 3.3×10^{-5} ℓ. mole^{-1} sec.$^{-1}$ (10). When optically active 1-bromobutane-1-d was maintained at 25° with lithium bromide in 90% aqueous acetone, it gradually racemized. From the optical rotation of the bromide used (α_0) and that recovered after time t (α_t), a second-order rate constant could be calculated from the relationship

$$k = \frac{2.303}{2C_{LiBr} \times t} \log \frac{\alpha_0}{\alpha_t} .$$

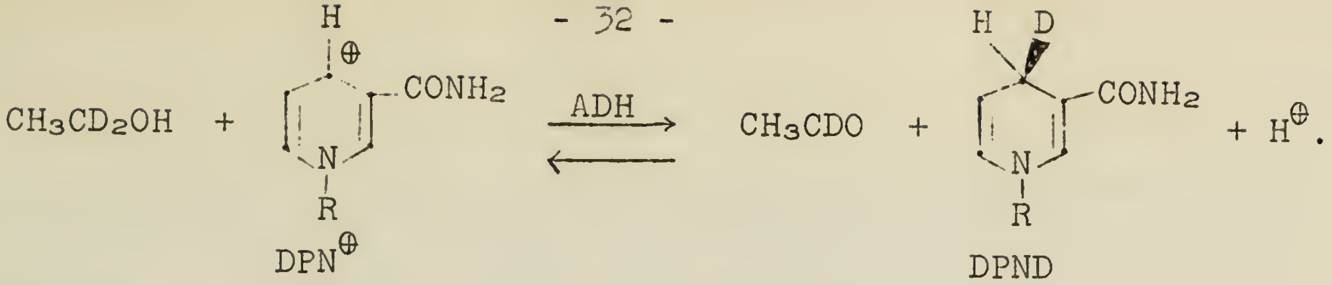
The weighted average of the results was $(3.0 \pm 0.5) \times 10^{-5}$ ℓ. mole^{-1} sec.$^{-1}$, in good agreement with the previous data.

Optically active benzyl-α-d alcohol having $[\alpha]^{20}D$ -0.645 ± 0.002° (neat) has been prepared by the partially stereospecific reduction of benzaldehyde-d with optically active isobornyloxymagnesium bromide (11). The optical activity was definitely associated with the deuterobenzyl system by conversion of the optically active alcohol to the bromide. Of several methods of preparation, that giving the highest yield of bromide with the highest optical activity was the reaction of the alcohol with an equimolar quantity of phosphorus tribromide. The second-order rate constants for the racemization of the optically active bromide by bromide ion, and the exchange with radioactive bromide ion agreed within experimental error.

Streitwieser, Wolfe, and Schaeffer have assigned relative configurations to benzyl-α-d alcohol and 1-butanol-1-d by converting them both to 1-phenylbutane-1-d using reactions of known or presumed stereochemistry (12).

ENZYMATIC SYNTHESIS OF THE ENANTIOMORPHS OF ETHANOL-1-d

Westheimer and his coworkers have shown that in the oxidation of ethanol by diphosphopyridine nucleotide ($DPN^{\oplus}$) in the presence of yeast alcohol dehydrogenase (ADH), hydrogen or deuterium is transferred directly and reversibly from the α-carbon of the ethanol to $DPN^{\oplus}$ (13) according to the equation,



Furthermore, it was shown that the transfer was stereospecific for the reduced carbon atom of the DPN$^{\oplus}$.

In subsequent investigations these workers have demonstrated that the enzymatic reduction of acetaldehyde is stereospecific (14). One enantiomorph of ethanol-1-d was prepared by oxidizing enzymatically reduced DPND with acetaldehyde in the presence of alcohol dehydrogenase. Equations (a)--(d) summarize the preparation and analysis of this ethanol.

$$\mathrm{CH_3CD_2OH} + \mathrm{DPN}^{\oplus} \overset{\text{ADH}}{\rightleftarrows} \mathrm{CH_3CDO} + \underline{\mathrm{DPND}} + \mathrm{H}^{\oplus} \qquad (a)$$

$$\mathrm{CH_3CHO} + \mathrm{DPND} + \mathrm{H}^{\oplus} \overset{\text{ADH}}{\rightleftarrows} \underline{\mathrm{CH_3CHDOH}} + \mathrm{DPN}^{\oplus} \qquad (b)$$

$$\mathrm{CH_3CHDOH} + \mathrm{DPN}^{\oplus} \overset{\text{ADH}}{\rightleftarrows} \mathrm{CH_3CHO} + \underline{\mathrm{DPND}} + \mathrm{H}^{\oplus} \qquad (c)$$

$$\mathrm{CH_3COCOO}^{\ominus} + \mathrm{DPND} + \mathrm{H}^{\oplus} \overset{\text{LDH}}{\rightleftarrows} \underline{\mathrm{CH_3CDOHCOO}^{\ominus}} + \mathrm{DPN}^{\oplus} \qquad (d)$$

LDH = lactic dehydrogenase

Ethanol-1-d of the opposite configuration was prepared by oxidizing ordinary enzymatically reduced DPNH with deuterated acetaldehyde. The preparation and analysis of this ethanol are summarized by equations (e)--(g).

$$\mathrm{CH_3CH_2OH} + \mathrm{DPN}^{\oplus} \overset{\text{ADH}}{\rightleftarrows} \mathrm{CH_3CHO} + \mathrm{DPNH} + \mathrm{H}^{\oplus} \qquad (e)$$

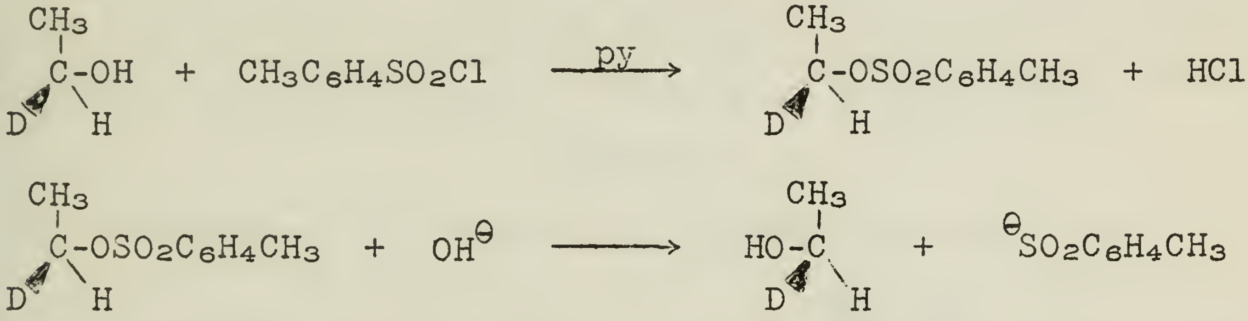
$$\underline{\mathrm{CH_3CDO}} + \mathrm{DPNH} + \mathrm{H}^{\oplus} \overset{\text{ADH}}{\rightleftarrows} \underline{\mathrm{CH_3CDHOH}} + \mathrm{DPN}^{\oplus} \qquad (f)$$

$$\mathrm{CH_3CDHOH} + \mathrm{DPN}^{\oplus} \overset{\text{ADH}}{\rightleftarrows} \underline{\mathrm{CH_3CDO}} + \mathrm{DPNH} + \mathrm{H}^{\oplus} \qquad (g)$$

In both sequences the underlined compounds were isolated in the form of suitable derivatives and analyzed for deuterium. Although neither stereoisomer, prepared by these means, was obtained in sufficient quantity to permit a polarimetric determination of optical rotation, the stereochemical purity of each isomeric alcohol was demonstrated by observing the specific products of its enzymatic reoxidation. For example, the ethanol-1-d prepared from ordinary acetaldehyde and DPND (equation b) was shown to give only ordinary acetaldehyde on reoxidation, and to transfer deuterium to the DPN$^{\oplus}$ to form DPND (equation c). This deuterium was proven to be present in the DPND molecule in the reduced position by making a further transfer to pyruvate in the presence of lactic dehydrogenase (equation d) and showing that the deuterium appeared in the lactate which was formed.

In contrast, the ethanol-1-*d* prepared from deuteroacetaldehyde and ordinary DPNH (equation f) gave deuteroacetaldehyde on reoxidation by $DPN^{\oplus}$ (equation g). These clear differences in the behavior of the alcohols have been taken as proof by Westheimer and his coworkers that each of the alcohols consists of one pure enantiomorph of ethanol-1-*d* and that the enantiomorphs have opposite configurations

As a further means of proving the existence of enantiomorphs of opposite configuration, the inversion of one enantiomorph of ethanol-1-*d* was accomplished by the following series of reactions:



It was assumed that the formation of the tosylate occurred without inversion, since the asymmetric center was not involved, and that in the saponification, carried out in strong alkali, inversion occurred. The inversion was shown by the fact that before the above reactions, the ethanol-1-*d* reacted enzymatically with $DPN^{\oplus}$ to give deuteroacetaldehyde and DPNH, whereas after these reactions it gave ordinary acetaldehyde and DPND under the same conditions.

More recently, gram quantities of a pure enantiomorph of ethanol-1-*d* have been prepared by the reduction of deuteroacetaldehyde with glucose in the presence of alcohol dehydrogenase, glucose dehydrogenase and a catalytic amount of $DPN^{\oplus}$ (15). This alcohol was shown to contain no more than 0.1% of its enantiomorph and to possess an optical rotation of $[\alpha]^{28}D$ -0.28 ± 0.03° (neat).

SOLVOLYSIS OF 1-BUTYL-1-*d* *p*-BROMOBENZENESULFONATE

(-)-1-Butanol-1-*d* having $[\alpha]^{25}D$ -0.036 ± 0.002° (neat) when converted to (+)-butyl-1-*d* acetate with acetyl chloride in pyridine, followed by alkaline hydrolysis, regenerated (-)-butanol-1-*d* with $[\alpha]^{25}D$ -0.033 ± 0.009° (neat) (8). The formation of the ester is assumed not to have affected the asymmetric center, thus the overall retention of configuration in the cycle indicates that the alkaline hydrolysis also did not affect the asymmetric center.

(-)-Butanol-1-*d* of the above optical rotation was allowed to react with *p*-bromobenzenesulfonyl chloride in pyridine to form (+)-butyl-1-*d* *p*-bromobenzenesulfonate having $[\alpha]^{25}D$ 0.015 ± 0.003° (neat). Solvolysis of this brosylate at 99.4° in acetic acid gave (-)-butyl-1-*d* acetate. As indicated by the change in sign of rotation of the acetate, a net inversion of configuration had taken place. The average of a large number of determinations of rotation showed 96 ± 8% inversion, any racemization being too small to detect. Comparable results were obtained in the formolysis of the brosylate which showed 92% inversion of configuration.

SOLVOLYSIS OF 1-BUTYL-1-d p-NITROBENZENESULFONATE

Solvolysis of 1-butyl-1-d p-nitrobenzenesulfonate in acetic acid at 114° produced 1-butyl-1-d acetate with 85 ± 2% net inversion (16). Control experiments showed the starting material to be recoverable from a partial solvolysis with no loss of optical activity and the product acetate to be stable under the reaction conditions. On the basis of these results it was concluded that at least 15% racemization occurred which was due neither to racemization of the starting material nor the product but to a property of the solvolysis reaction itself.

Solvolyses of optically active 1-butyl-1-d p-nitrobenzenesulfonate were run in mixtures of acetic acid and nitrobenzene, dioxane, and o-dichlorobenzene. Table I gives a summary of the results which show that the addition of either dioxane or nitrobenzene to the acetic acid caused increased racemization. The addition of o-dichlorobenzene, by contrast, caused increased inversion of configuration.

TABLE I

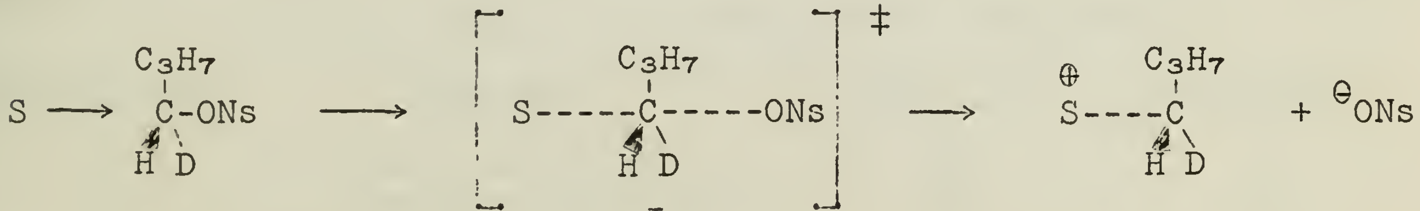
Acetolyses of 1-Butyl-1-d p-Nitrobenzenesulfonate

Solvent	Temp., °C	No. of 1/2-lives	% Net Inversion
Glacial Acetic Acid	114.4	~22	85 ± 2
90% $C_6H_5NO_2$ -10% CH_3COOH	114.4	1.5	51 ± 2
90% $C_6H_5NO_2$ -10% "	90.8	1.4	59 ± 2
75% Dioxane -25% "	97.1	1.2	47 ± 2
75% o-$C_6H_4Cl_2$ -25% "	97.1	~ 3	94 ± 6

Control experiments again indicated that in all cases the racemization observed was unequivocally a result of the solvolytic displacement itself. The possibility that racemization arose from the intervention of olefin was ruled out on the basis that no secondary acetates were detectable in any of the reaction products.

PROPOSED MECHANISMS

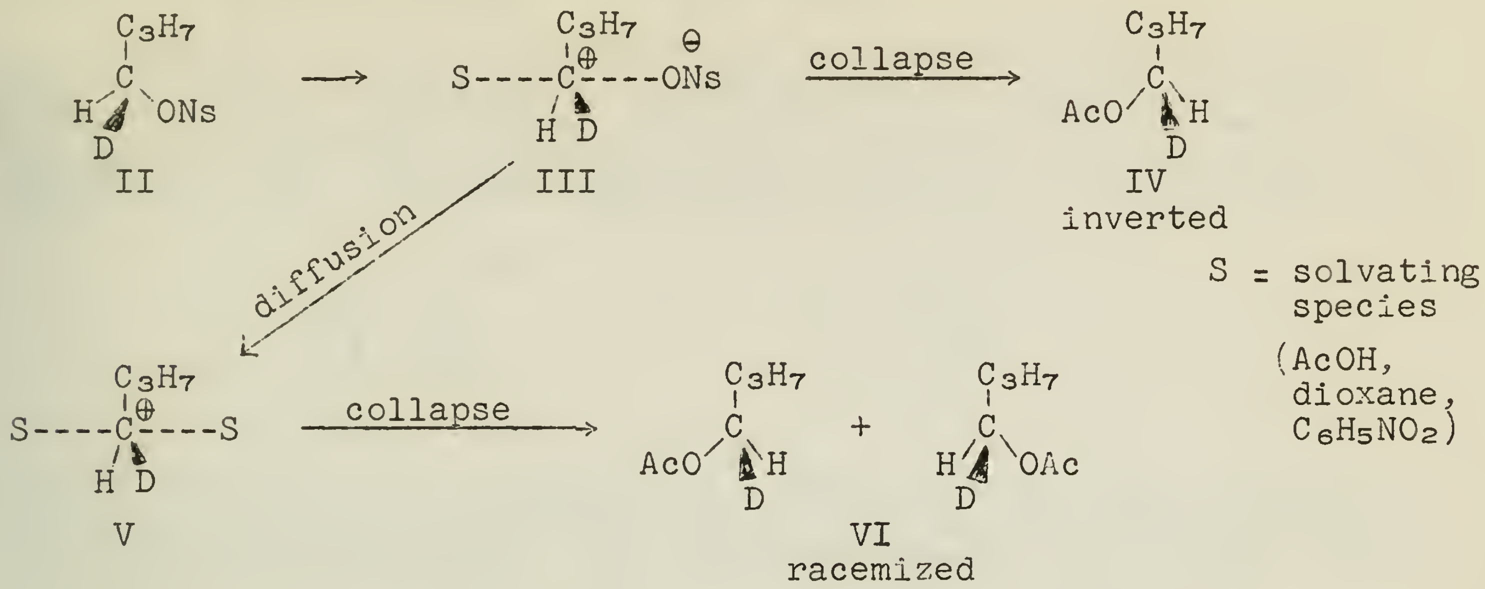
The fact that displacements were accompanied by little or no racemization in pure acetic acid would be consistent with a direct displacement by solvent involving a structure such as I as a transition state, where S represents the acetic acid molecule and ONs the leaving group, p-nitrobenzenesulfonate. Whereas there is evidence that such a mechanism is operative in solvolysis by such strongly nucleophilic solvents as ethanol and water (17,18), this is not likely the case for solvents of the low nucleophilicity of acetic acid and formic acid.



I

Alternatively, if the solvolyses are not of the direct displacement type, the existence of an intermediate may be postulated (8). The demonstration of racemization has become accepted evidence for the involvement of a symmetrically solvated carbonium ion. Thus, from the results of the solvolysis in glacial acetic acid, it may be postulated

that at least 15% of the reaction went through an intermediate. Assuming that all of the reaction went through an intermediate, Streitwieser has invoked a mechanism in which the rate determining step leads to an intermediate covalently solvated ion-pair such as III



Following its formation the intermediate ion-pair may collapse to give the inverted product IV, or it may become symmetrically solvated as in V and go on to racemic product VI. The function of added nucleophiles such as dioxane and nitrobenzene is to increase the lifetime of the carbonium ion intermediate leading to greater diffusion of the ion-pair III prior to its collapse, resulting ultimately in a greater proportion of racemization. Added solvents such as o-dichloro benzene possessing no free electron pairs are incapable of competing effectively with acetic acid in solvating the carbonium ion intermediate, and thus a product representing almost complete inversion results.

In the absence of added nucleophiles the observed lack of racemization may be accounted for in terms of the relative instabilities of the intermediates III and V, whose primary carbon atoms are incapable of delocalizing positive charge effectively. Thus, the intermediate ion-pair III is very unstable relative to the solvolysis product IV having normal bonding, and diffusion leading to the formation of the intermediate V is unfavored in the weakly nucleophilic solvent acetic acid. The importance of the nucleophilicity of solvent in the case of primary, as compared with secondary and tertiary systems, is seen in the accompanying table of solvolysis rates. These results have

TABLE II

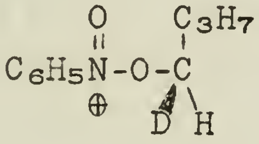
Solvolyses Ratios for Ethanol and Acetic Acid

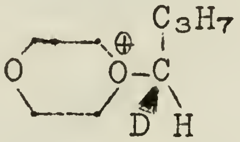
k_{EtOH}/k_{AcOH}	Substrate	Temp., °C	Reference
39	Ethyl Tosylate	75	19
3.8	Isopropyl Brosylate	75	19
0.43	t-Butyl Chloride	70	20

been explained (8) on the basis that the ability to distribute charge is increased for the secondary and tertiary systems and that the increased nucleophilicity of ethanol becomes unimportant in these cases.

It is of interest to compare Streitwieser's work on the solvolysis of primary compounds with the acetolysis of a secondary system, α-chloroethylbenzene (21). Here the product was formed with 15% net inversion and 85% racemization, indicating that at least 85% of this reaction proceeded through an intermediate.

Although a direct displacement by acetic acid does not accommodate the facts, nitrobenzene or dioxane may be pictured as taking part in a direct displacement reaction on the p-nitrobenzenesulfonate to yield the unstable intermediates VII and VIII with inversion of configuration (16). A second displacement by acetic acid then gives the


VII

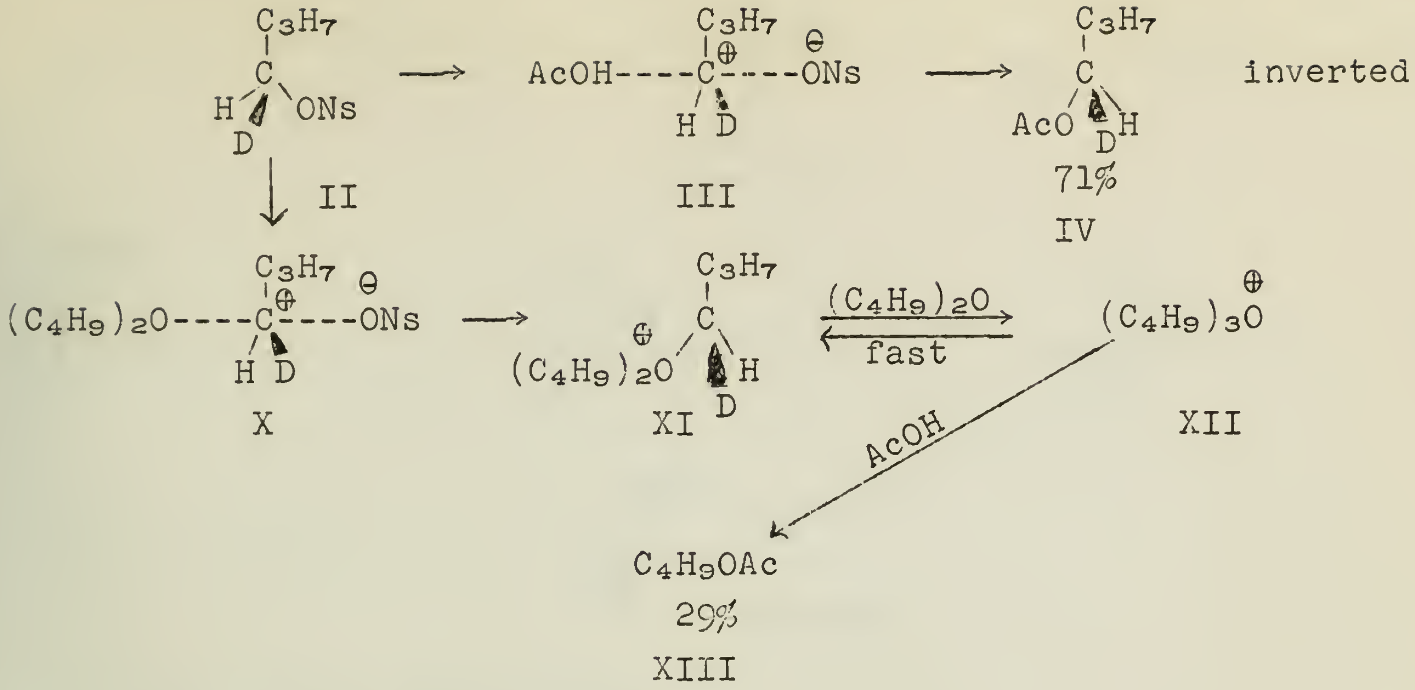

VIII

acetate with retained configuration. This retained ester, combined with the inverted ester from the direct reaction of acetic acid with the p-nitrobenzenesulfonate (cf. reaction sequence II ⟶ III ⟶ IV) would lead to the effective result of increased racemization.

Streitwieser and Andreades have carried out solvolyses of optically active 1-butyl-1-d p-nitrobenzenesulfonate in dibutyl ether-acetic acid mixtures to evaluate the importance of such structures (22). The solvolysis in 55% dibutyl ether-45% acetic acid at 100° gave a product acetate which had undergone, on the basis of optical rotation, an apparent net inversion of 42.5%. However, the acetate was found to have lost 56% of its deuterium, or, the 1-butyl-1-d acetate actually present was formed with 97 ± 6% inversion of configuration disallowing for its dilution with undeuterated 1-butyl acetate also formed during the reaction.

Dibutyl ether was used as the solvent in this reaction because if the corresponding oxonium ion (XI) was formed as an intermediate, its subsequent reaction with acetic acid would be noted by at least partial reaction at the undeuterated butyl group to give undeuterated 1-butyl acetate.

Under the reaction conditions employed 38% of the total product resulted from the direct cleavage of the dibutyl ether by p-nitrobenzenesulfonic acid formed in the acetolysis. Of the remaining 62% of the total product which resulted from the sulfonate solvolysis itself, 71% was formed without loss of deuterium (IV) and with 97% net inversion of configuration; the remaining 29% was formed with loss of deuterium (XIII). Streitwieser and Andreades conclude that the latter material could have arisen only from the intervention of the oxonium ion XI as a discrete but unstable intermediate. As indicated by the nearly complete inversion of configuration in the deuterated acetate, relatively little of this oxonium ion could have reacted with acetic acid directly for this would lead to an appreciable amount of racemized deuterated acetate. A reaction sequence which satisfactorily accounts for these facts involves an oxonium ion XI which undergoes a rapid and virtually complete exchange of deuterium with solvent. The non-deuterated tributyl oxonium ion XII then undergoes attack by acetic acid to give the non-deuterated butyl acetate.

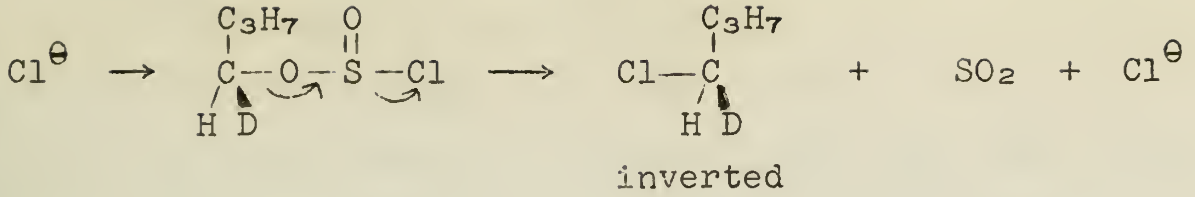


THE DECOMPOSITION OF OPTICALLY ACTIVE 1-BUTYL-1-*d* CHLOROSULFITE

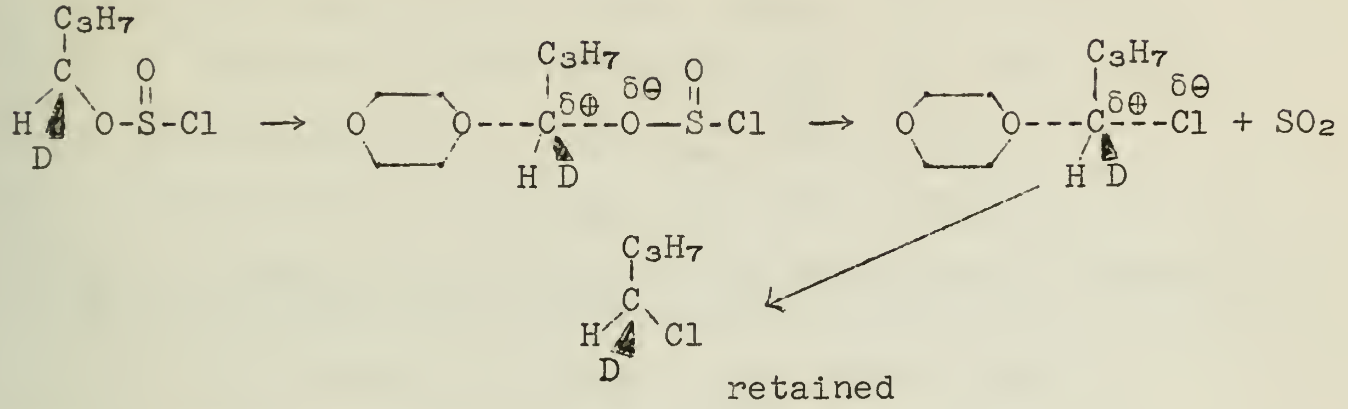
Optically active 1-butyl-1-*d* chlorosulfite has been prepared by the reaction of thionyl chloride and optically active 1-butanol-1-*d* (23). The thermal decomposition of this chlorosulfite in the absence of solvent resulted in a 45% yield of 1-butyl-1-*d* chloride. The chloride was converted to the acetate with tetramethylammonium acetate in acetone, such conditions being expected to give complete inversion. The optical purity of this acetate, as compared with 1-butyl-1-*d* acetate prepared directly, showed that the chloride was formed from the decomposition of the chlorosulfite with 91 ± 3% inversion of configuration. 1-Butyl-1-*d* chlorosulfite, not specially purified by distillation, when decomposed in dioxane solution at 83° resulted in 1-butyl-1-*d* chloride formed with 72 ± 4% net inversion of configuration. In contrast, the chlorosulfite specially purified by distillation and decomposed in dioxane solution at 84° resulted in the chloride formed with 33 ± 3% net inversion. An effective decrease in the degree of net inversion was thus obtained in the decomposition using starting materials of greater purity. The decomposition of the impure chlorosulfite apparently proceeded more rapidly as indicated by a marked evolution of sulfur dioxide.

Boozer and Lewis have carried out a particularly careful study of the thermal decomposition of alkyl chlorosulfites (24) and have suggested an intermediate carbonium ion-chlorosulfite ion ion-pair. These workers found that the decomposition of chlorosulfites in dioxane resulted in almost complete retention of configuration. Presumably the dioxane solvates the ion-pair from the rear and the displaced chlorosulfite ion decomposes to give the chloride ion which displaces the dioxane by "internal return".

Chlorosulfite decomposition has been found by Lewis and Coppinger (25) to be catalyzed by the chloride ion. Thus the greater amount of inversion obtained from the decomposition of the unpurified 1-butyl-1-*d* chlorosulfite, as well as the increased rate, may be explained on the basis that chloride ion is present as an impurity. The chloride ion catalyzed decomposition and the decomposition of the purified chlorosulfite are shown in reaction sequences (h) and (i) respectively.



(h)



(i)

OPTICALLY ACTIVE 1-AMINOBUTANE-1-*d*

Optically active 1-aminobutane-1-*d* has been prepared by the reaction of optically active butyl-1-*d* brosylate with an excess of sodium azide in methanol (26). 1-Butyl-1-*d* azide was not isolated but was reduced directly in ether solution with lithium aluminum hydride to give a 70% overall yield of 1-aminobutane-1-*d* having $[\alpha]^{25}_{D}$ -0.009 ± 0.003° (neat). No completely stereospecific method of converting an amine of this type to the corresponding alcohol as a means of checking the optical purity was available. Since the asymmetric center was not involved in the preparation of the brosylate, no loss of optical activity is expected in this step. The direct displacement by the azide ion is likewise not expected to result in any appreciable racemization. Again in the reduction by lithium aluminum hydride the asymmetric center is not involved.

The possibility of salt formation with the azide which would lead to racemization *via* a resonance stabilized carbanion of the type

$$\mathrm{R}\overset{\ominus}{\mathrm{C}}\mathrm{H}-\mathrm{N}=\overset{\oplus}{\mathrm{N}}=\overset{\ominus}{\mathrm{N}} \longrightarrow \mathrm{RCH}=\mathrm{N}-\mathrm{N}=\overset{\ominus}{\mathrm{N}}$$

was ruled out on the basis of a control experiment involving the synthesis of 1-aminobutane-1,1-d_2 by the same sequence of steps. The product was found to contain the same amount of deuterium as the starting material. Had salt formation occurred deuterium would have been lost.

As a final means of proving the stereospecificity of the reaction, the procedure was applied to optically active 2-octanol. The stereochemical relationship of 2-octylamine, which is known (27), indicated that the conversion went with less than 3% loss of optical activity.

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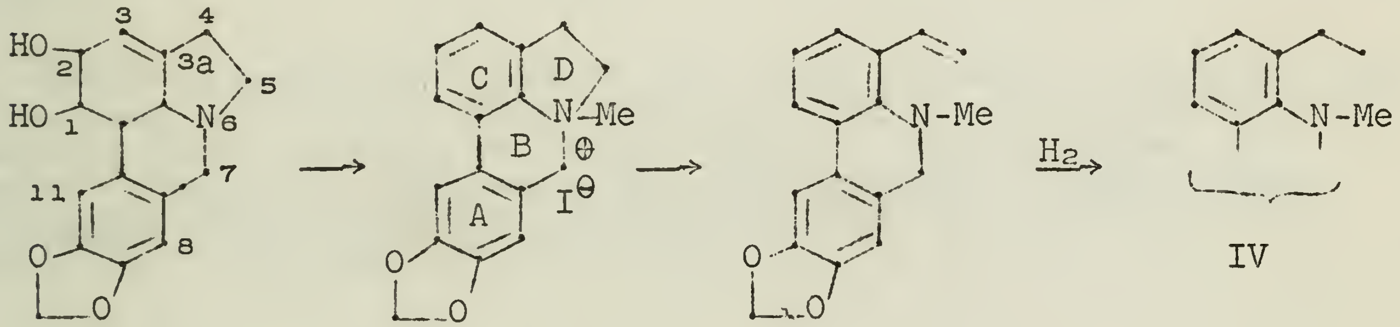
AMARYLLIDACEAE ALKALOIDS

Reported by John A. Hedge March 16, 1959

The Amaryllidaceae alkaloids may be divided roughly into six classes, according to their basic skeletons. Examples of these six classes are lycorine (I), tazettine (XXXIV), crinine (XL), homolycorine (LXIII), galanthamine, and belladine.

STRUCTURE OF LYCORINE

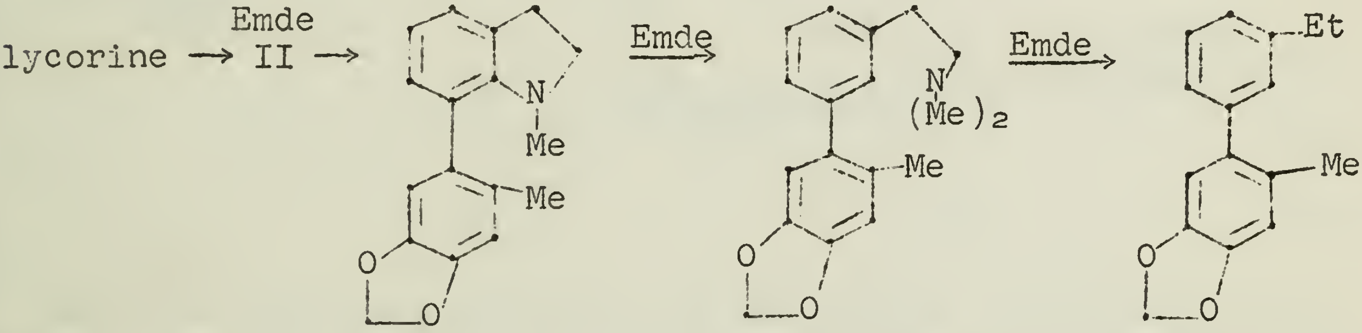
Lycorine (I), $C_{16}H_{17}NO_4$, is the most abundant and widespread alkaloid of the Amaryllidaceae group. Lycorine yields phenanthridine upon zinc dust distillation. Hofmann degradation of lycorine gives lycorine anhydromethine (III) (1). Anhydrolycorine methiodide (II) is an intermediate (2). Synthetic II also gives III (3). Hydrogenation of compound III gives the base IV, which has been synthesized (4



IV

I II III

Lycorine, through II, yields lycorine anhydrohydromethine (V) by Emde degradation. Lycorine anhydrohydromethine (V) forms a hexahydro derivative upon catalytic hydrogenation. Emde degradation of V gives VI which upon Emde degradation gives VII. Dihydrolycorine (XI) is stable to Emde degradation (2).



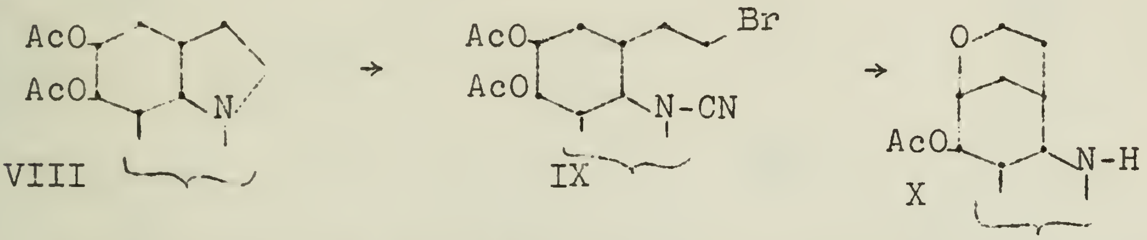
V VI VII

The above degradations are best explained if both the hydroxyls and the double bond are in the C ring. The two hydroxyls are vicinal and secondary, as shown by lead tetraacetate cleavage and stability in acid (2). The double bond is not conjugated with the aromatic ring as shown by the ultraviolet spectrum (1). The double bond is not α,β to the nitrogen atom (lycorine pK'_a 6.4, dihydrolycorine pK'_a 8.4 (5)).

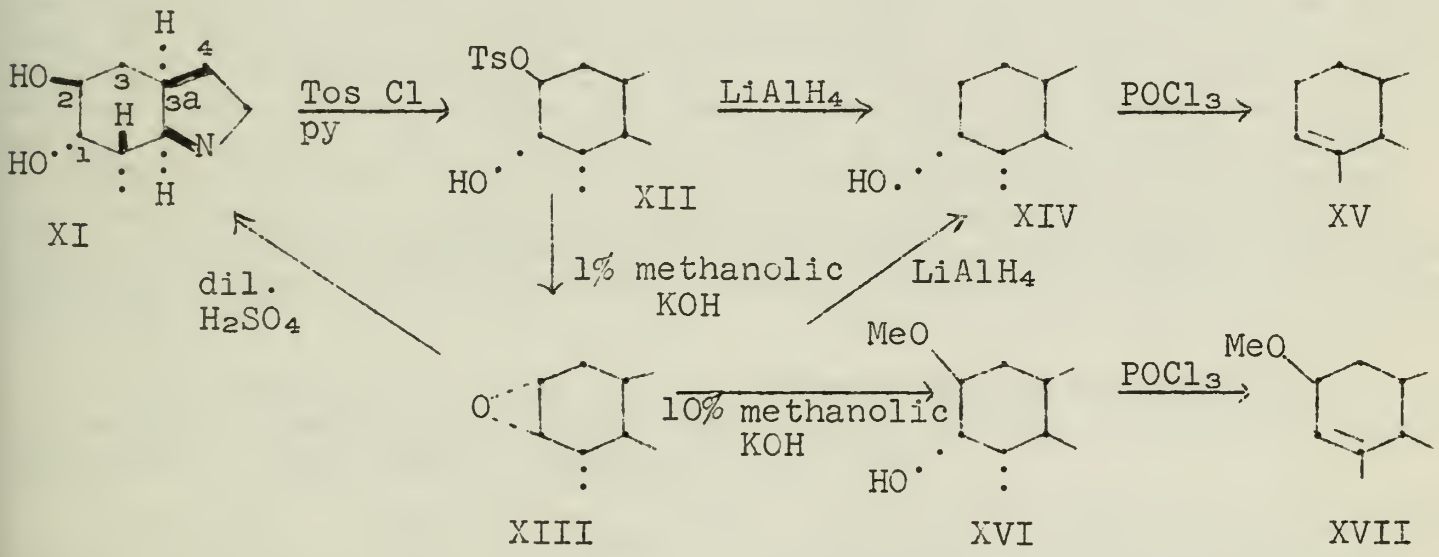
Vinyl tertiary amines are more basic than their saturated analogs (6). The infrared spectrum shows bands characteristic of a trisubstituted double bond (7). A 3a,4-double bond, exocyclic to a six-membered ring, would be expected to rearrange in acid and so is ruled out (8). Thus, since the hydroxyls are vicinal, secondary, and non-enolic, the double bond must be in the 3,3a-position (2).

STEREOCHEMISTRY OF DIHYDROLYCORINE

Treatment of diacetyldihydrolycorine (VIII) with cyanogen bromide gives IX, which upon alkaline hydrolysis gives an ether monoacetate (X). Thus the C_2 hydroxyl and the D-ring ethylene residue must be on the same side of the C ring (9).



Dihydrolycorine (XI) treated with tosyl chloride in pyridine gives the monotosylate (XII). The monotosylate (XII) heated in 1% methanolic potassium hydroxide gives an epoxide (XIII), which is opened with dilute sulfuric acid, regenerating dihydrolycorine. Such openings give trans-diaxial hydroxyls, thus proving that the hydroxyls of dihydrolycorine are trans and axial (10,11).

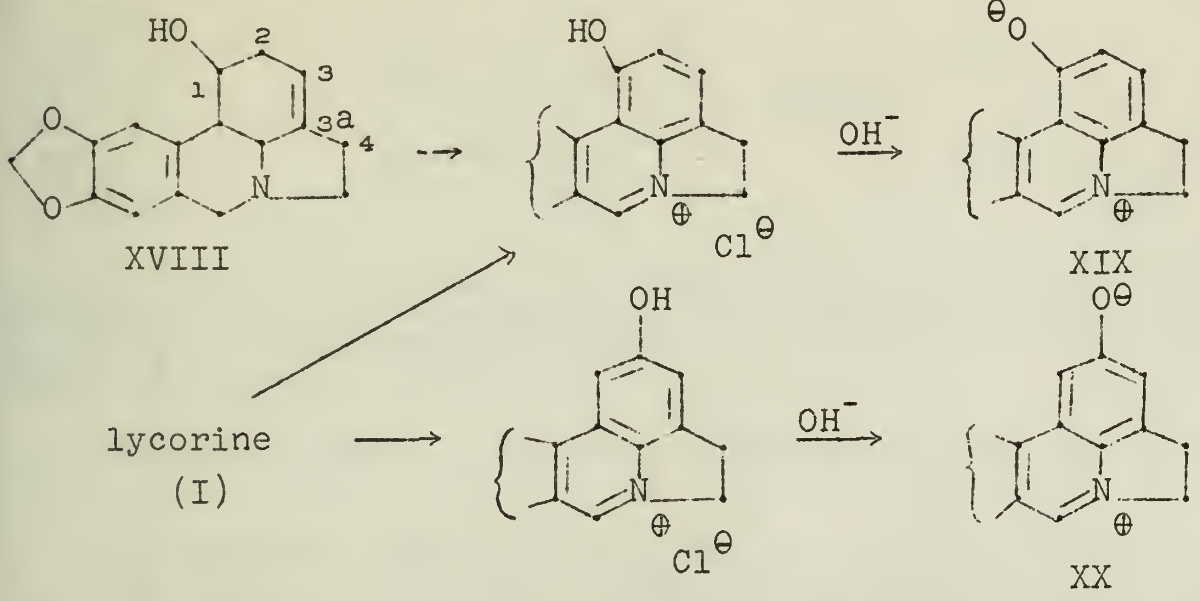


Both the monotosylate (XII) and the epoxide (XIII) give monodesoxydihydrolycorine (XIV) (α-dihydrocaranine) upon treatment with lithium aluminum hydride. Treatment of XIV with phosphoryl chloride gives XV which has a double bond conjugated with the aromatic ring. Treatment of XIII with 10% methanolic potassium hydroxide gives XVI, which by dehydration with phosphoryl chloride is converted to XVII (11). Both eliminations indicate that the benzylic hydrogen must be axial and trans to the axial C_1 hydroxyl.

Since the C_2 hydroxyl is axial, the ethylene residue of the D ring in X must also be axial. Therefore, the D ring must be cis-fused to the C ring, since trans-diaxial fusion is sterically impossible. From the elimination reactions giving XV and XVII, it is shown that the benzylic hydrogen is axial to ring C, and therefore the B ring must be trans-fused to the C ring (10,11).

OTHER ALKALOIDS WITH THE BASIC LYCORINE STRUCTURE

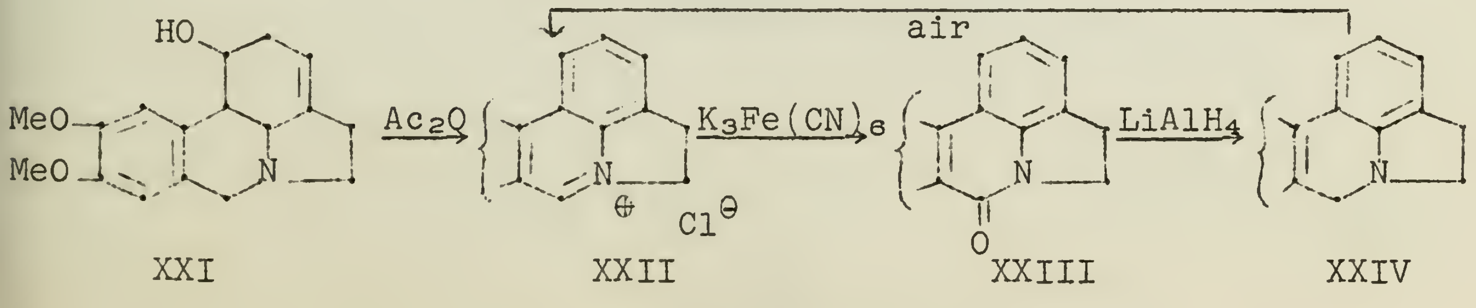
CARANINE. Caranine (XVIII) (12) gives XIX as the sole product upon modified Oppenauer oxidation. Lycorine gives XX by SeO_2 oxidation, while mercuric acetate oxidation of lycorine gives both XX and XIX (proven by spectral models). Thus the hydroxyl of caranine is at C_1 (13).



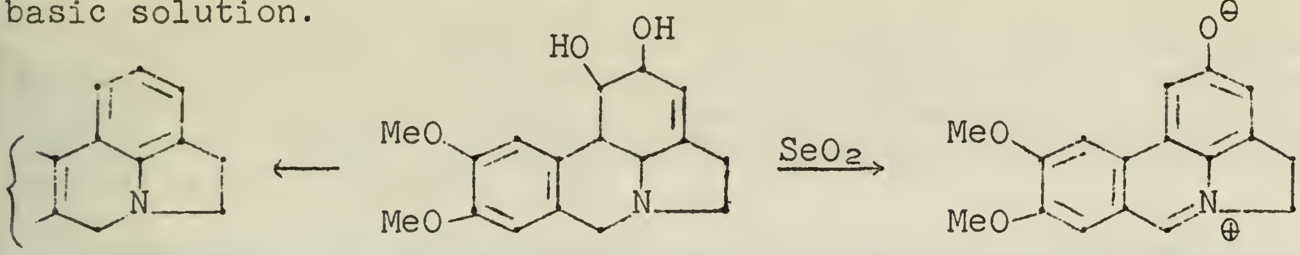
Hydrogenation of caranine over platinum in acetic acid gives α-dihydrocaranine (same as monodesoxydihydrolycorine (XIV)), while hydrogenation over palladium in ethanol gives β-dihydrocaranine (14). The isolation of two isomers on hydrogenation requires that the double bond of caranine be at least trisubstituted. The double bond is not conjugated with the aromatic ring, is not α,β to the nitrogen atom (no strong adsorption of either the perchlorate or the acetyl derivative in the 6_u region (15)), and is not part of an allyl alcohol system since caranine does not give an α,β-unsaturated ketone on manganese dioxide oxidation. Since the hydroxyl is secondary and non-enolic, the two remaining possibilities for the double bond position are 3,3a and 3a,4. The 3a,4 possibility is ruled out on the same basis as for lycorine (14).

The structure of caranine is confirmed by the conversion of lycorine to caranine with sodium and n-amyl alcohol by direct hydrogenolysis of the allylic hydroxyl group (16).

PLUVIINE. Oxidation of pluviine (XXI) with potassium permanganate gives m-hemipinic acid (XXXIII). Pluviine was therefore postulated as the dimethoxy analog of caranine (XVIII)(17). Acetic anhydride and pluviine give acetylpluviine and XXII. Compound XXII is oxidized to XXIII (17), which has been synthesized (18). Reduction of XXIII gives XXIV (18), which is converted to XXII on air oxidation in methanolic hydrochloric acid (17).



METHYLPSEUDOLYCORINE. Methylpseudolycorine (XXV) dissolved in dilute base, concentrated to dryness, and heated under reduced pressure, yields XXIV, which has been synthesized (18) and has also been obtained from pluviine. Selenium dioxide oxidation gives XXVI, which has an ultraviolet spectrum very similar to XX (from lycorine) in basic solution.



XXIV XXV XXVI

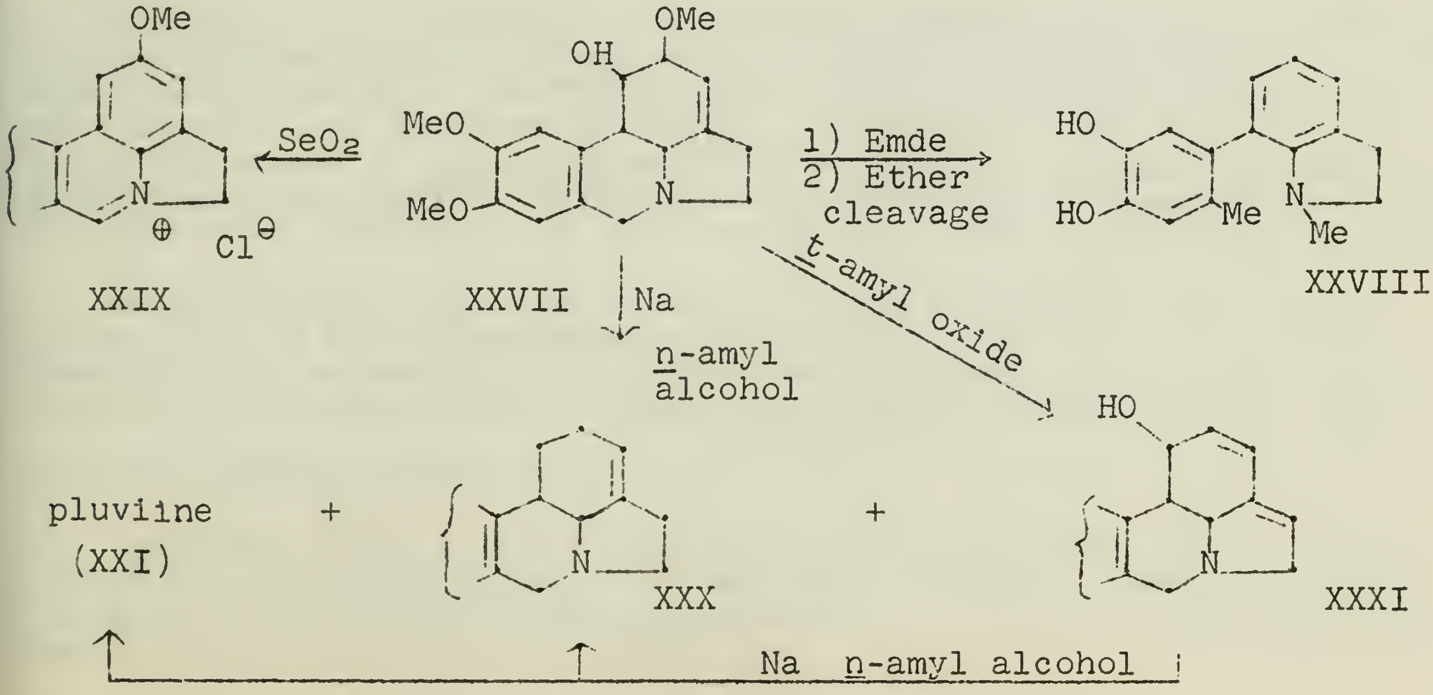
A 3,3a-position for the double bond is required on the same grounds as for caranine and lycorine. Thus the second hydroxyl must be at C_1, and accordingly, methylpseudolycorine is the dimethoxy analog (XXV) of lycorine (18).

Pseudolycorine (1,59) gives methylpseudolycorine on methylation (18).

GALANTHINE. Galanthine (20,21,18) (XXVII) gives reactions which parallel those of lycorine. Emde degradation followed by ether cleavage gives XXVIII, which is also obtained by similar treatment of lycorine (21). Pyrolysis gives XXIV, which has also been obtained from methylpseudolycorine and pluviine (22). Oxidation with selenium dioxide gives a quaternary base chloride (XXIX) which does not give a free betaine in basic solution. The ultraviolet spectrum of XXIX was nearly identical with that of the salt of XXVI in acid solution. Thus the aliphatic methoxyl was proven to be at C_2 (22).

Acid hydrolysis of galanthine gives methylpseudolycorine (16).

Treatment of galanthine with sodium and n-amyl alcohol gives pluviine (XXI), methylpseudolycorene (XXX), and a small amount of dehydromethylpseudolycorine (XXXI). The dienol (XXXI) was also prepared by treatment of galanthine with potassium t-amyl oxide in t-amyl alcohol.

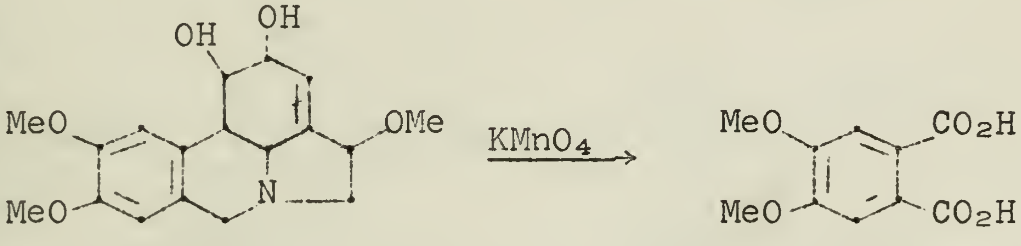


XXIX XXVII XXVIII XXX XXXI

On treatment with sodium and n-amyl alcohol the dienol yields pluviine and XXX. The dienol is therefore probably an intermediate in the reaction of galanthine with sodium and n-amyl alcohol. The dienol may react by cleavage of the allylic hydroxyl followed by 1,4-reduction to give XXX, or may react by 1,4-reduction to give pluviine (16).

NARCISSIDINE. Narcissidine (19) (XXXII), like methylpseudolycorine, lycorine, and galanthine, is oxidized by both selenium dioxide and mercuric acetate; however, the products quickly darken and are not useful. Oxidation with potassium permanganate gives m-hemipinic acid (XXXIII) (16).

Treatment of narcissidine with sodium and n-amyl alcohol gives the same products as were obtained from galanthine (16).



XXXII XXXIII

FALCATINE. The infrared spectrum of falcatine shows a strong 1600 cm^{-1} band characteristic of an aromatic ring containing both a methylenedioxy group and a methoxyl group (23). Treatment of falcatine with sodium and isoamyl alcohol gives caranine (XVIII), proving that falcatine is ar-methoxycaranine (16).

TAZETTINE

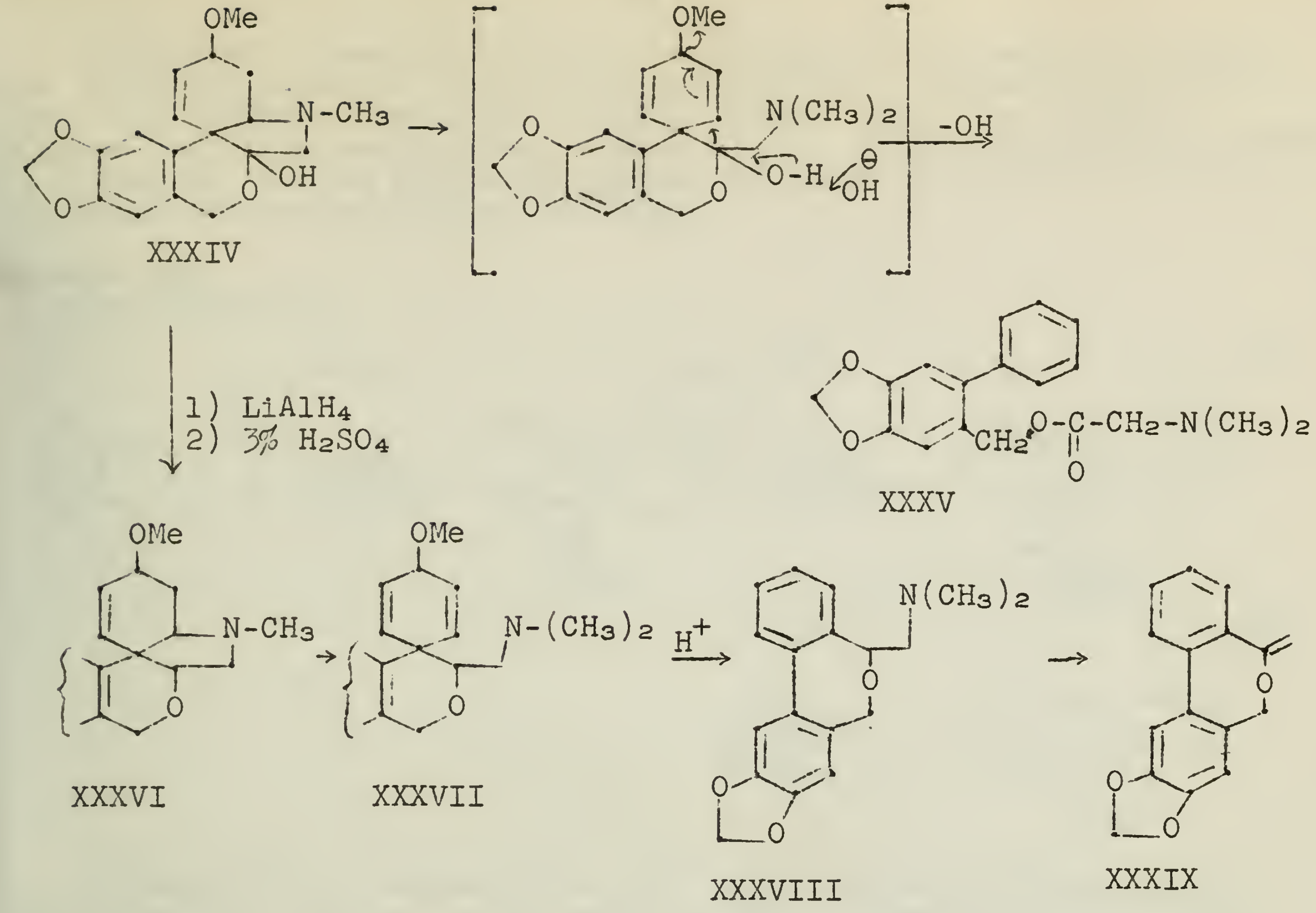
Tazettine (XXXIV), $C_{18}H_{21}NO_5$, on zinc dust distillation yields phenanthridine and on oxidation yields hydrastic acid (1). Tazettine undergoes Hofmann degradation yielding an intermediate methine which undergoes base-catalyzed aromatization (24,25) to form tazettine methine (XXXV)(26). Tazettine methine (XXXV) has been synthesized from 6-phenylpiperonyl alcohol, chloroacetyl chloride, and dimethylamine (26).

Reduction of tazettine with lithium aluminum hydride (27) followed by acid cyclization (28) gives deoxytazettine (XXXVI) (24,25) (anhydrotazettadiol). Deoxytazettine (XXXVI) undergoes Hofmann degradation to give the methine XXXVII, which rearranges in acid at room temperature to neo-methine XXXVIII (24,25). Hofmann degradation of XXXVIII gives XXXIX. Oxidation of XXXIX gives 4,5-methylenedioxydiphenyl -2,2'-dicarboxylic acid, which has been synthesized (25,28).

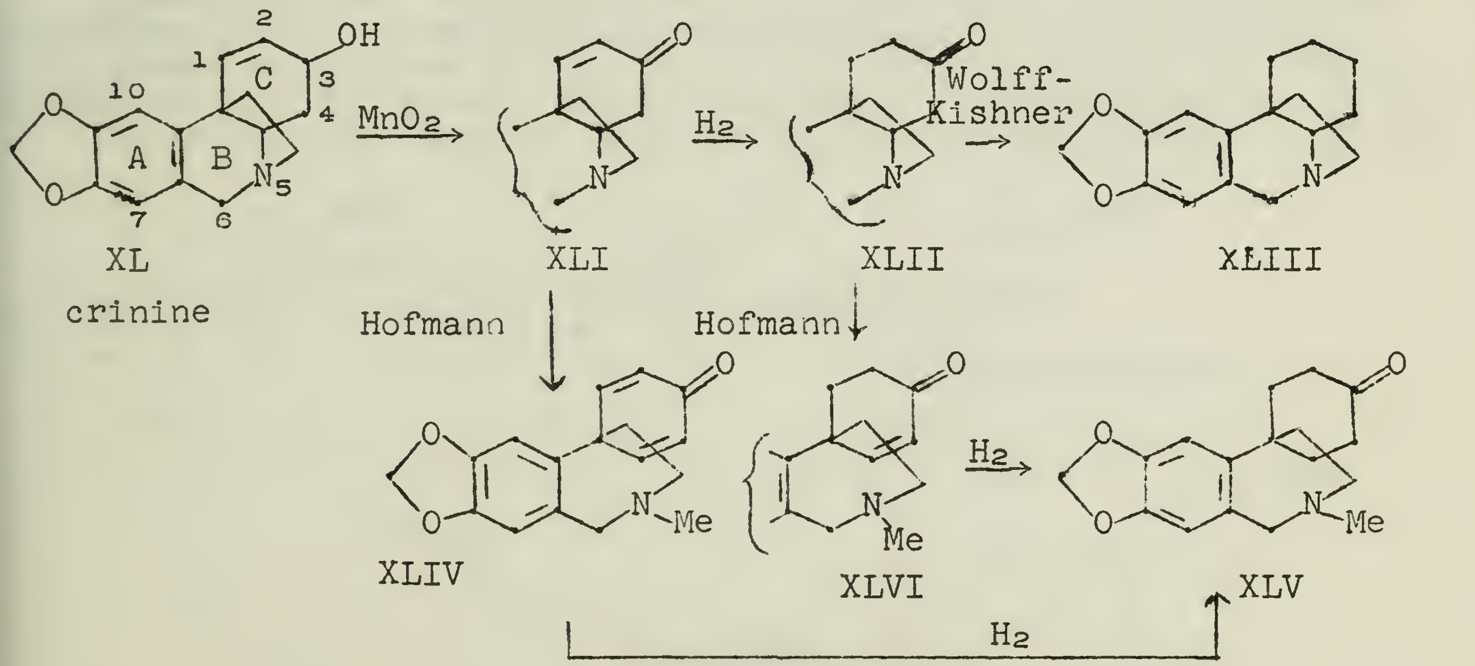
Haemanthidine (29) yields tazettine on treatment with methyl iodide (30) or with formaldehyde and formic acid (31) and so was thought to be N-demethyltazettine; however, haemanthidine has been found to be 6-hydroxyhaemanthamine (see haemanthamine section (58).

ALKALOIDS OF THE CRININE TYPE

CRININE. Crinine (12) (crinidine (32)), $C_{16}H_{17}NO_3$,(XL) is not affected by selenium dioxide and mercuric acetate. These are useful reagents for the pyrrolo[de]phenanthridine (lycorine) type alkaloids. Ring C of crinine resists aromatization (33).

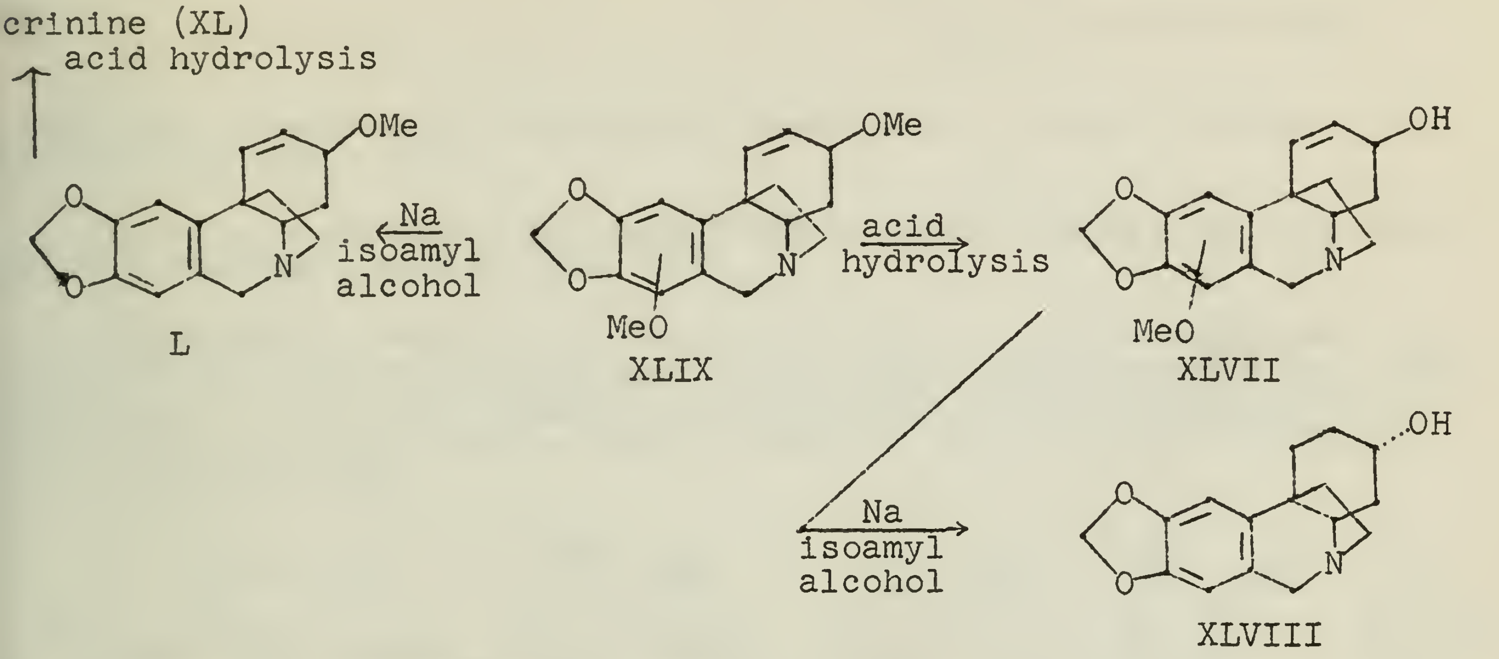


Oxidation with manganese dioxide gives an α,β-unsaturated ketone, oxocrinine (XLI). Catalytic hydrogenation of XLI gives XLII. Mild Wolff-Kishner reduction of XLII gives l-crinane (60) (XLIII), which has been synthesized (33,34).



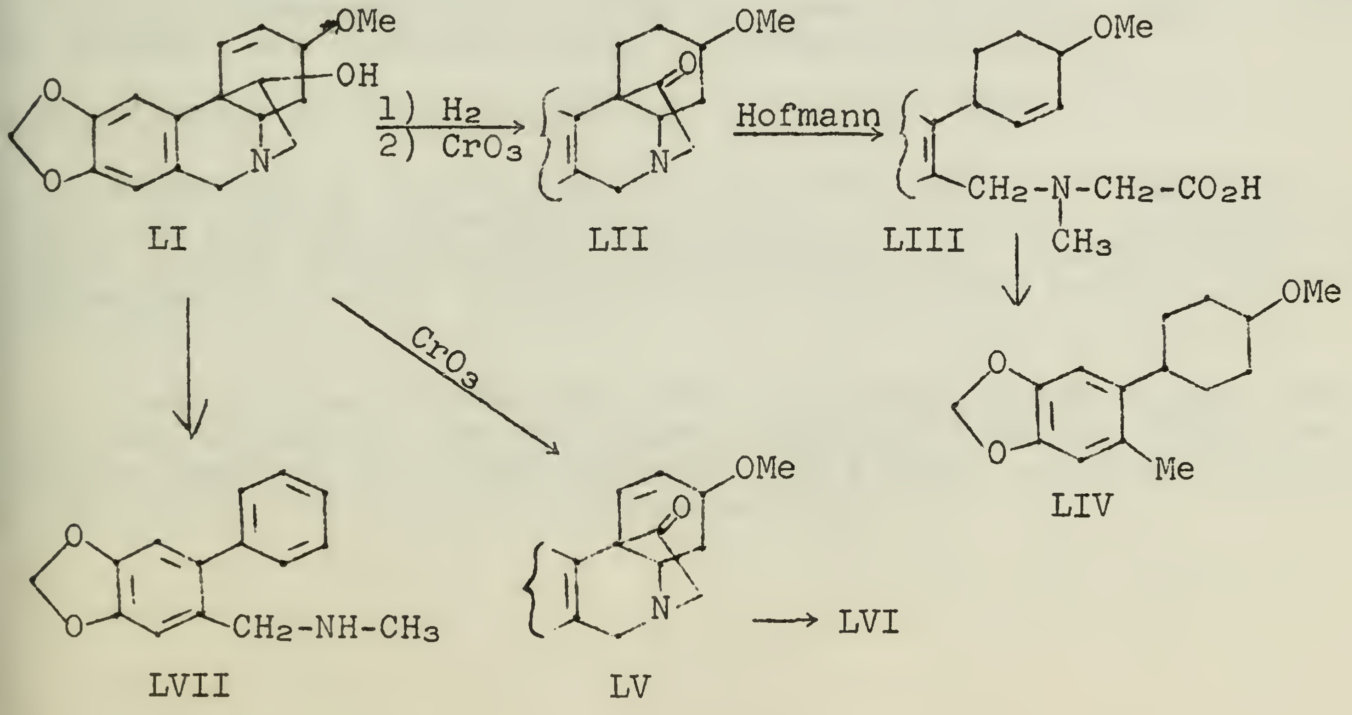
Hofmann degradation of oxocrinine (XLI) gives the methine XLIV with extreme ease, and it was found that this reaction was a special case of β-elimination from a β-aminoketone. Catalytic hydrogenation of XLIV gives XLV. Both XLIV and XLV are optically inactive. Hofmann degradation of XLII gives an optically active methine XLVI, which on hydrogenation gives XLV (33).

POWELLINE. Powelline (XLVII), $C_{17}H_{19}NO_4$, is *ar*-methoxycrinine. Its reactions parallel those of crinine (33,36). Treatment of powelline with powdered sodium and isoamyl alcohol gives two isomeric olefins and dihydroepicrinine (XLVIII) (16). Dihydroepicrinine (XLVIII) is formed by lithium aluminum hydride reduction followed by catalytic hydrogenation of oxocrinine (XLI)(33).



BUPHANIDRINE. Buphanidrine (37) XLIX on mild acid hydrolysis gives powelline and so is the methyl ether of powelline (16,33,36). Powdered sodium and isoamyl alcohol convert buphanidrine to buphanisine (37) (L) by de-*ar*-methoxylation (16). Acid hydrolysis of buphanisine gives crinine (XL)(16).

HAEMANTHAMINE. Haemanthamine (29,38,60)(LI) on zinc dust distillation gives 6,7-methylenedioxyphenanthridine (39). Catalytic hydrogenation followed by chromic acid oxidation give LII. Hofmann degradation of LII yields the methine LIII. Catalytic hydrogenolysis of LIII gives LIV. Chromic acid oxidation of haemanthamine gives LV,



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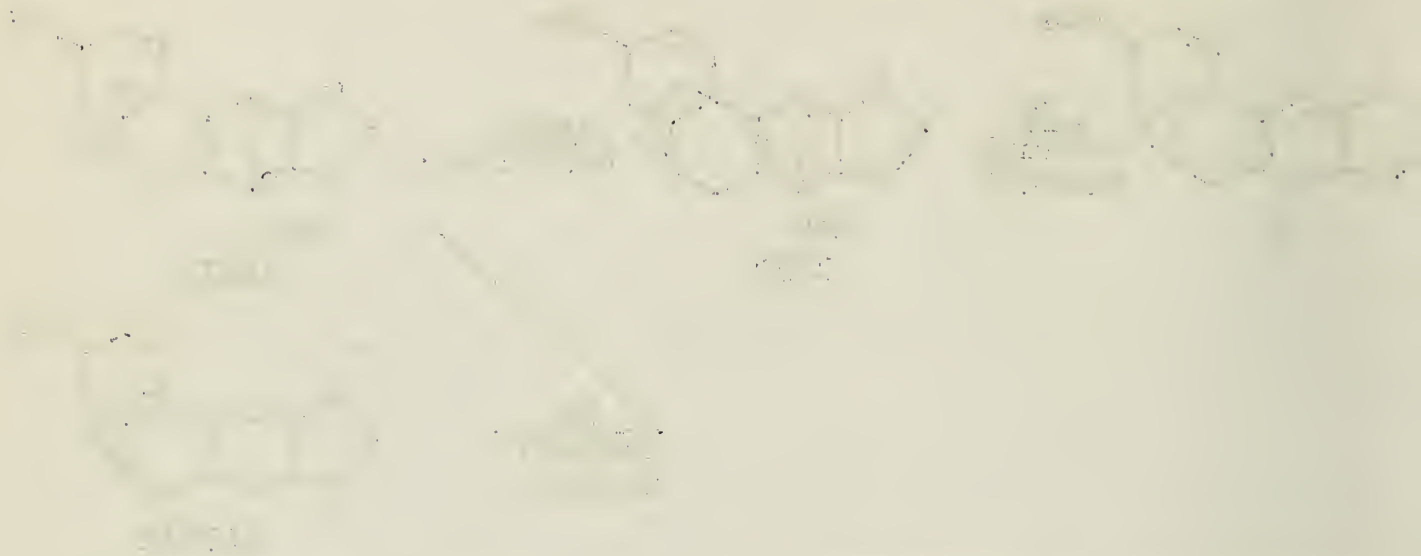

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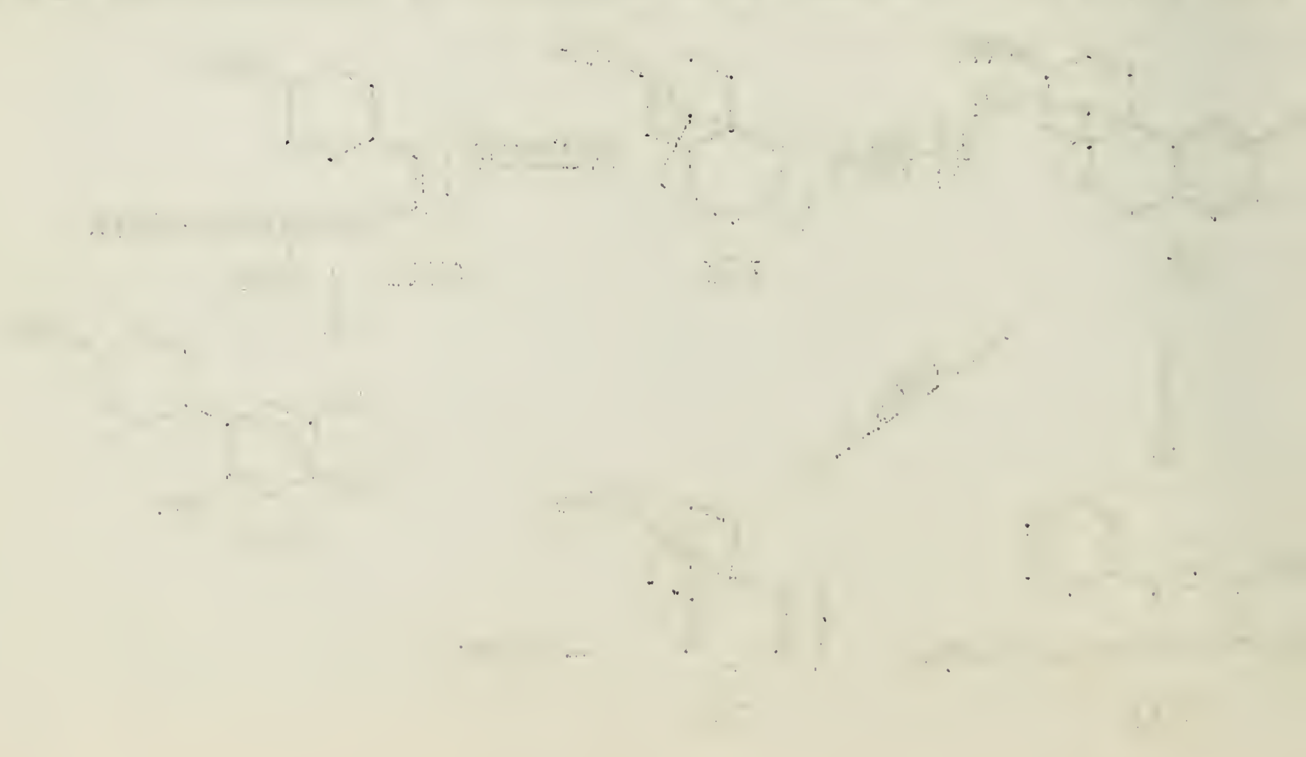
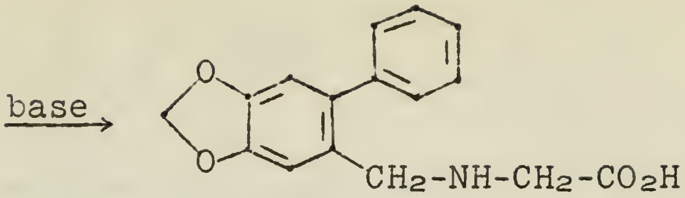


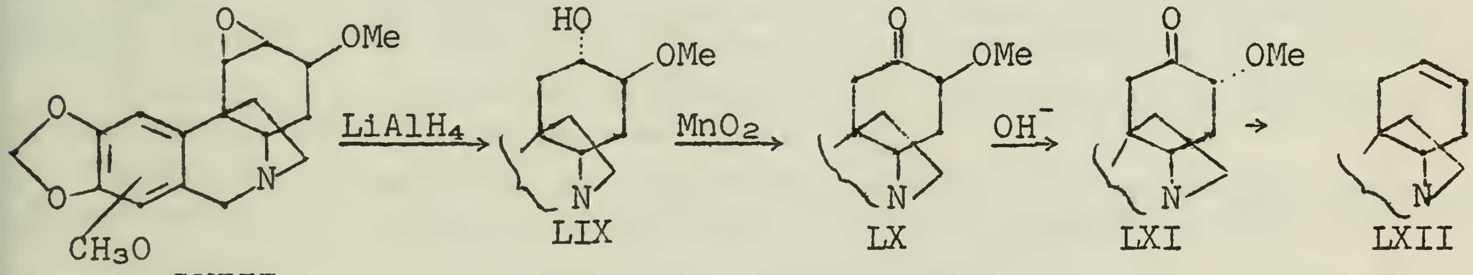


LVI

which when treated with potassium *t*-butoxide in *t*-butyl alcohol gives LVI (synthesized) (40).

Hofmann degradation of haemanthamine itself gives a mixture which on acid treatment yields LVII (39).

UNDULATINE. Undulatine (41)(LVIII) has an epoxide ring which is opened with lithium aluminum hydride to give α-dihydroundulatine (LIX). Oxidation of LIX with manganese dioxide gives oxo-α-dihydroundulatine (LX) which is epimerized in base giving LXI, in which the methoxyl group is equatorial.



LVIII LIX LX LXI LXII

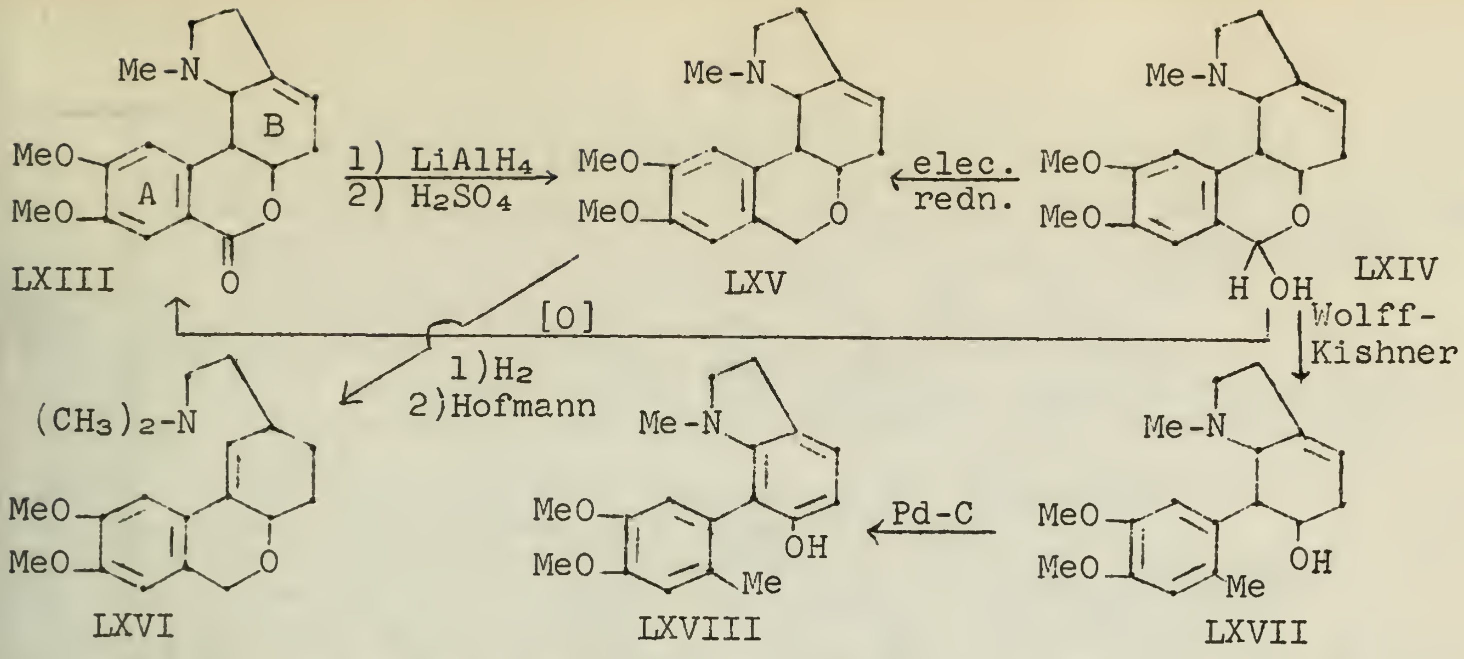
Wolff-Kishner reduction of LXI gives the olefin LXII. This olefin formation proves that the hydroxyl and methoxyl are vicinal in α-dihydroundulatine. Hydrogenation of the olefin gives (+)-powellane. The mesylate of α-dihydroundulatine gives buphanidrine (XLIX) when refluxed with potassium *t*-amyl oxide in *t*-amyl alcohol (41).

Both haemanthamine (LI) and crinamine (1,12) yield haemultine (42,43) on treatment with sodium and *n*-amyl alcohol. Thus, crinamine is probably the methoxyl epimer of haemanthamine (40).

ALKALOIDS OF THE HOMOLYCORINE AND LYCORENINE TYPE

Homolycorine (1,44)(LXIII), $C_{18}H_{21}NO_4$, has a six-membered lactone ring (45) showing infrared absorption at 1712 cm^{-1}. Lycorenine (1) (LXIV) yields homolycorine on permanganate (45), chromic acid (46), and manganese dioxide oxidation (47), and so must have a lactol structure.

Homolycorine on treatment with lithium aluminum hydride and cyclization with dilute acid gives α-desoxylycorenine (LXV) (reactions parallel to tazettine)(46). This ether was also obtained by electrolytic reduction of lycorenine (48).



Hofmann degradation of dihydro-α-desoxylycorenine gives the methine LXVI, which has its double bond conjugated with the aromatic ring. This fixes the point of the nitrogen attachment to ring B (49).

Lycorenine undergoes a Wolff-Kishner reaction to give LXVII. Dehydrogenation of LXVII with palladium on charcoal gives the phenol LXVIII, thus fixing the point of the oxygen attachment to ring B (46).

Nerinine (32,35)(methoxylycorenine) on chromic acid oxidation gives albomaculine (50,51) (methoxyhomolycorine).

Neronine is oxidized by manganese dioxide to oxoneronine, which is) also formed from krigeine by manganese dioxide oxidation (51).

Oduline (52) gives masonine on oxidation (53).

Hippeastrine (54) on hydrogenation yields dihydrohippeastrine which is probably a diastereoisomer of clivonine (50,51).

ALKALOIDS OF THE GALANTHAMINE TYPE

Galanthamine (56), $C_{17}H_{21}NO_3$, chlidanthine (50), narcissamine (20), narwedine (18), Base IX (1,18), lycoramine (1), and irenine (55) are members of the fifth group. Their complete structures have not yet been established (55,56).

BELLADINE

Belladine, $C_{19}H_{25}NO_3$, is a possible precursor of other Amaryllidaceae alkaloids (57).

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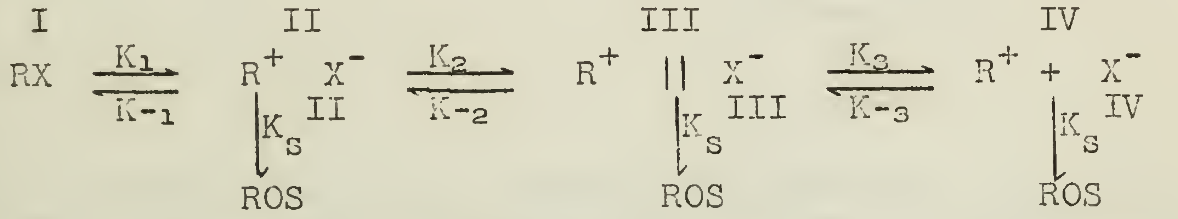
SALT EFFECTS AND ION PAIRS

Reported by J. A. Deyrup March 23, 1959

INTRODUCTION

On the basis of considerations to be discussed below, the dissociation of a covalent molecule in solvents of low dielectric constant might be expected to proceed through at least two ion pair stages. This seminar will examine the work, primarily by Winstein, in which these intermediate ion pair stages have been isolated kinetically.

PROCESS OF IONIZATION



$$\begin{tikzcd}[column sep=large]
\overset{\text{I}}{\text{RX}} \arrow[r, shift left, "K_1"] & \overset{\text{II}}{\text{R}^+\ \text{X}^-_{\ \text{II}}} \arrow[l, shift left, "K_{-1}"] \arrow[r, shift left, "K_2"] \arrow[d, "K_s"] & \overset{\text{III}}{\text{R}^+\ ||\ \text{X}^-_{\ \text{III}}} \arrow[l, shift left, "K_{-2}"] \arrow[r, shift left, "K_3"] \arrow[d, "K_s"] & \overset{\text{IV}}{\text{R}^+ + \text{X}^-_{\ \text{IV}}} \arrow[l, shift left, "K_{-3}"] \arrow[d, "K_s"] \\
 & \text{ROS} & \text{ROS} & \text{ROS}
\end{tikzcd} \qquad (1)$$

The ionization of covalent molecule I must be due to the stabilization of the resultant ion pair (II) by solvation, thus offsetting the increase in energy accompanying charge separation. In this resulting peripherally-solvated ion pair, the ions are only partially separated from each other. For this reason, it has been referred to as an intimate or internal ion pair.[1] Furthur separation of II would require the input of additional energy until separation becomes sufficient to allow each ion to be individually solvated. This pair of ions in two separate solvent cages,[2] still in the force field of each other, is termed a solvent-separated ion pair (III).[3] Finally, complete separation by the pair of ions, again requiring additional energy, gives the dissociated species IV. It may be useful to consider this entire process in terms of the following schematic energy diagram.[4]

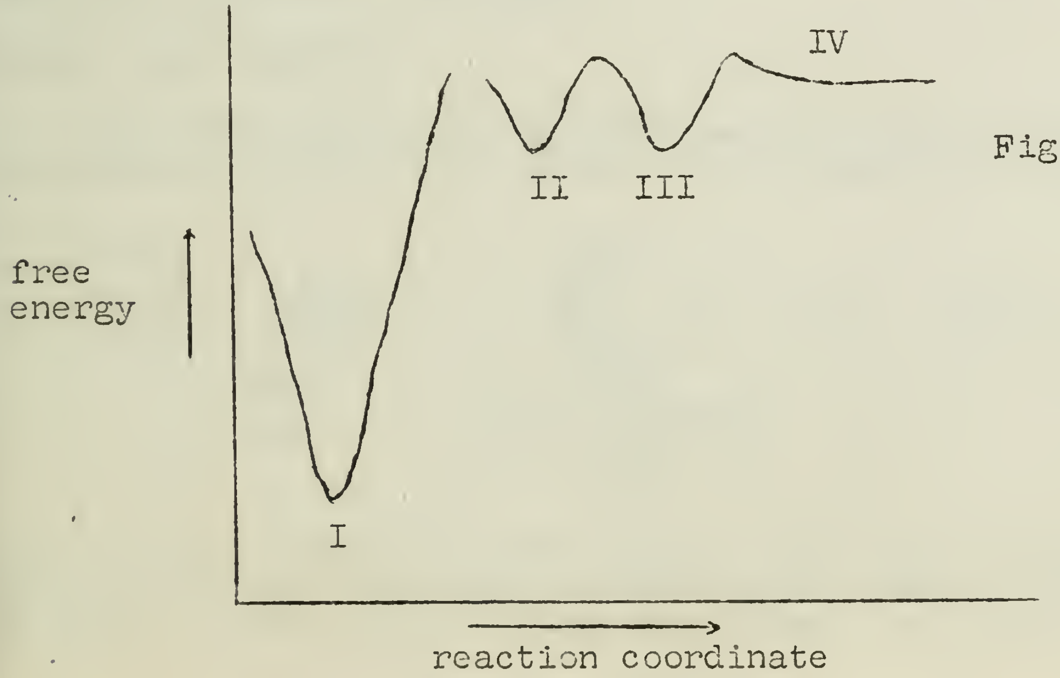
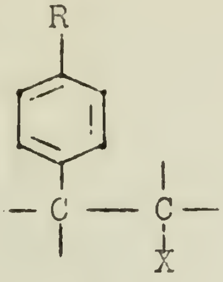
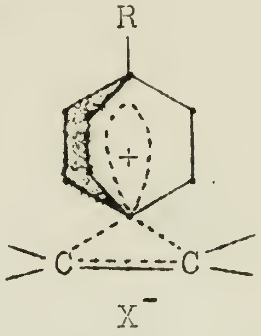


Fig. 1

The remainder of this seminar will be concerned with the experimental evidence demonstrating the necessity to consider ion pairs II and III (in addition to the dissociated ions IV) in solvolysis. The systems which Winstein has found most useful are those which proceed with anchimerically assisted ionization to give bridged cations (VI).



V



VI

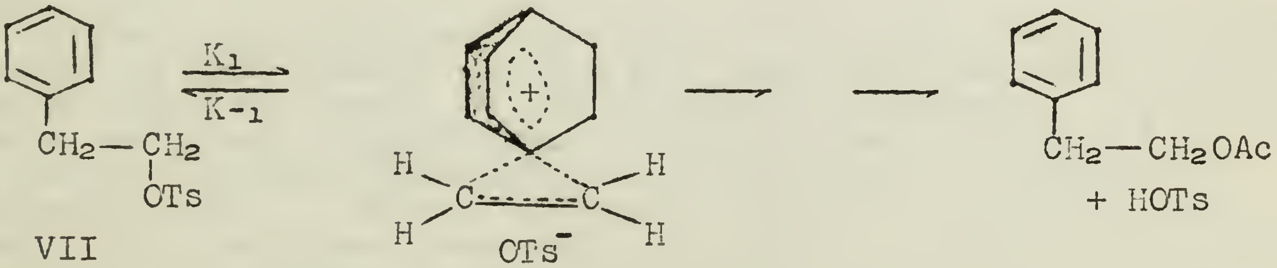
This sort of system permits the simplifying assumption that K_s^{II} is approximately equal to zero since backside attack of intimate ion pair II would be sterically hindered.[5] The validity of this assumption, however, must be considered in terms of Grunwald's work[6] which may show that front side attack on the intimate ion pair occurs in the solvolysis of 1-phenylethyl chloride. The fact that the ratio $K_1 / K_s^{II} + K_s^{III} + K_s^{IV}$ (to be discussed later) is relatively insensitive to changes in the solvent nucleophilicity,[5,7] would tend to justify the approximation that K_s^{II} is equal to zero.

SALT EFFECTS

The most useful information which has been obtained about the solvolytic scheme (1) arises from studying the effects of a variety of salts on compounds derived from V. The following sections will deal with these salt effects.

NORMAL SALT EFFECTS

The first system to be discussed here will be 2-phenylethyl p-toluenesulfonate VII.[8] Rates of solvolysis in acetic acid were



VII

measured by titration of the product, p-toluenesulfonic acid, with sodium acetate. The kinetics were first order in ester, even in the presence of added salt (except for common ion action as discussed below).

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As can be seen from Figure 2, the addition of salt causes a

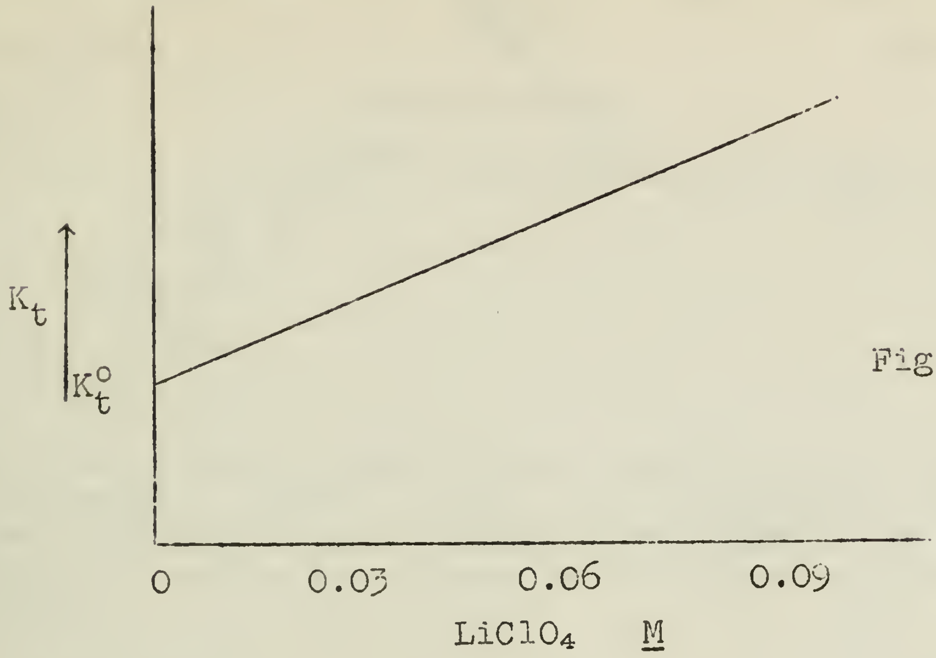


Fig. 2

linear increase in the titrimetric rate constant which is best fitted by the equation[9]

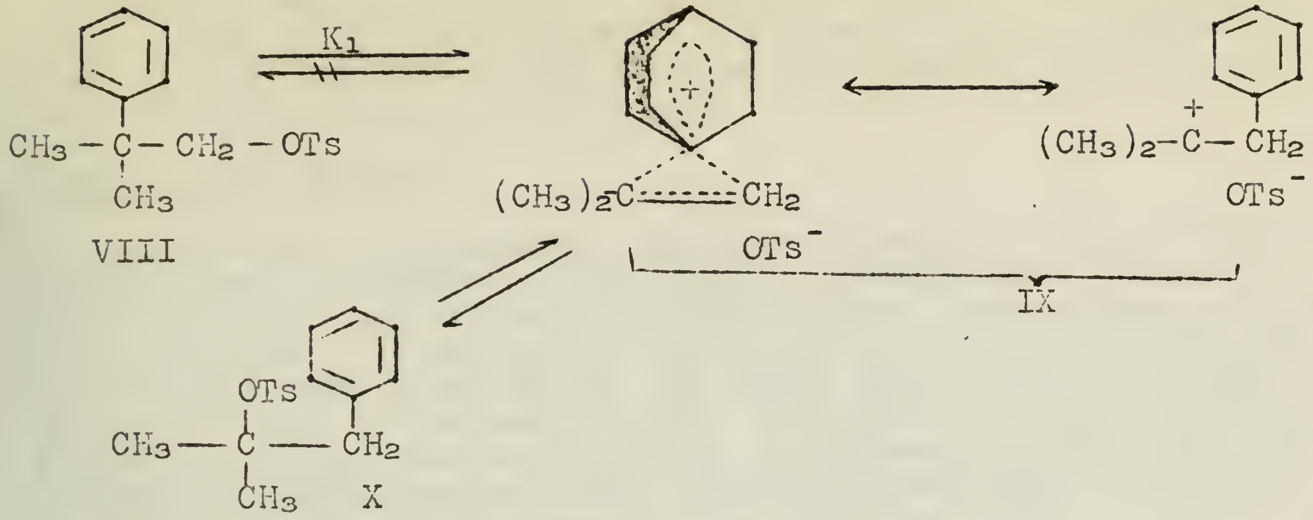
$$K_t = K_t^o\ (1 + b\ [LiClO_4]). \qquad (2)$$

Similar effects are associated with a number of salts, differing only in their individual value of b. Considering a typical case, that of cholesteryl p-toluenesulfonate,[10] the following values of b were obtained (at 50°).

TABLE I

$LiClO_4$	28
$HClO_4$	28
DPG (diphenylguanidinium) $HClO_4$	12
DPGHAc	6
LiOAc	2

Where tested, this order was observed for all the compounds showing this type of salt effect. It has also been observed that b varies inversely with the square of the absolute temperature.[9] Such salt effects, referred to by Winstein as "normal" salt effects,[9] are due to transition state stabilization by attraction of suitable ion atmospheres.[5,11] Linear increases of K_t with increasing salt concentration have been observed in a variety of similar compounds.[9] An interesting example is that of 2-methyl-2-phenylpropyl (neophyl) p-toluenesulfonate (VIII) which would give intimate ion pair (IX). Ion pair return from IX would give the reactive X which would



solvolyze immediately.[9] Experiments confirm that VIII also shows a normal salt effect similar to VII. It is apparent, therefore, that the normal salt effect is involved in an increase in the rate of ionization (K_1) and is not primarily an effect on the other intermediates.

COMMON ION EFFECTS

The equation (3) has satisfactorily described the solvolysis behavior of certain systems.[12]

$$RX \rightleftharpoons R^+ + X^- \qquad R^+ \xrightarrow{HOS} ROS + H^+ \qquad (3)$$

The predicted decrease of the solvolysis rate towards zero in the presence of increasing common ion, X^-, was observed. It is interesting to examine the role of the common ion in systems for which the energy barriers isolating the ion pairs are significant. A steady state treatment of scheme (1) gives the following expression for the rate:[13]

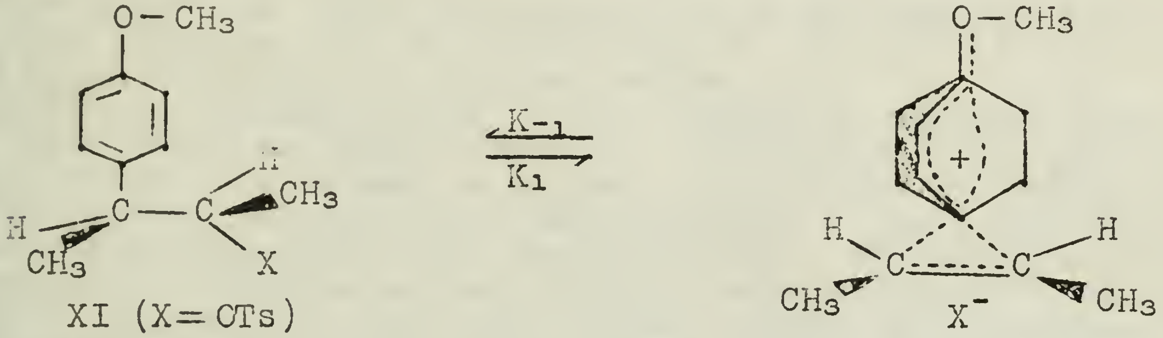
$$K_t = K_1 \Bigg/ 1 + \frac{\left[\dfrac{K_{-1}K_2}{K_s^{III} + K_s^{IV}\,\dfrac{K_3}{K_{-3}(X^-) + K_s^{IV}}}\right]}{\left[K_{-2} + K_s^{III} + \dfrac{K_3K_s^{IV}}{K_{-3}\,(X^-) + K_s^{IV}}\right]} \qquad (4)$$

Inspection of this equation shows that K_t does not approach zero as X^- becomes large. For those compounds of this series that show a common ion rate depression, e.g., 2-(2,4-dimethoxyphenyl)ethyl p-bromobenzenesulfonate,[13] the observed result of adding common ion is to effect only a partial reduction of K_t. Besides direct measurements of K_t in the presence of added common ion, the common ion

effect also manifests itself as a drift towards lower rate in the latter part of a kinetic run.[13] It should also be mentioned here that a large number of compounds in this series show no common ion rate depression, _e.g._ XI and XII.

SPECIAL SALT EFFECTS

Previously, an example was given in which the titrimetric rate constant was a measure of the rate of ionization. In cases in which there is significant internal return (defined as return of II to I), the rate of ionization would be expected to exceed the titrimetric rate constant on the basis of scheme (1). This is found to be the case in the acetic acid solvolysis of the optically active isomers of _threo_-_p_-anisyl-2-butyl p-toluenesulfonate (XI) and _p_-bromobenzenesulfonate (XII)[5] whose anchimerically assisted ionization produces the symmetrical ion pair XIII.

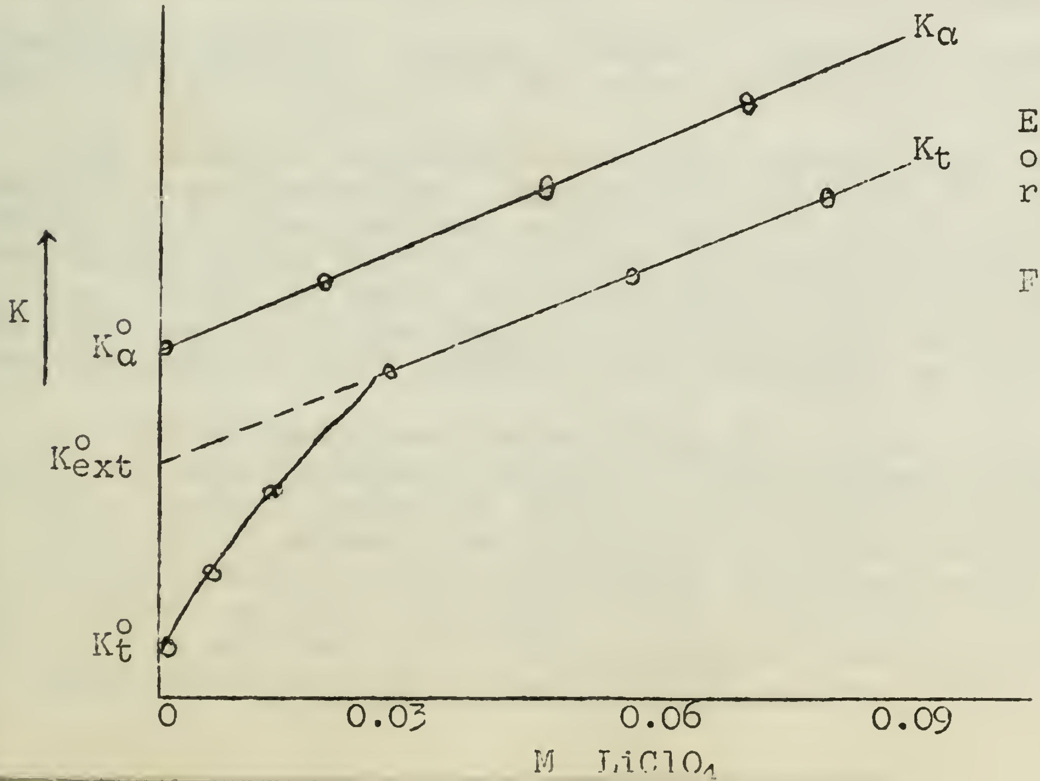


XI (X= OTs)
XII (X= OBs)

XIII

For this reason, the polarimetric rate constant, K_α, can be identified with the rate of ionization, K_1.

Considering that part of Figure 3 in which the concentration of lithium perchlorate is greater than 0.03 _M_, it is evident that the difference between K_α and K_t is due to internal return.[14] An alternative explanation[5] for the difference between K_α and K_t, based upon an independent cyclic mechanism, is not satisfactory.



Effect of $LiClO_4$ on the solvolysis rate of XII

Fig. 3

From Table II,[5] it can be seen that $K_\alpha^o - K_{ext}^o$ shows large variations in different solvents. This difference between K_α^o and K_{ext}^o could be associated with a possible independent cyclic rearrangement. A cyclic rearrangement, however, should be insensitive to variations in solvent ionizing power and nucleophilicity.[5]

Table II

Solvent effects on K_α^o and K_{ext}^o for XIII (25^o)

Solvent	$10^5\ K_\alpha^o$	$10^5\ K_{ext}^o$	$10^5\ (K_\alpha^o - K_{ext}^o)$
25% HCO_2H - HAc	6.56	6.08	0.48
HAc	80.6	19.6	61.0
EtOH	27.1	21.3	6.2
10% HCO_2H - dioxane	2.45	0.15	2.30

From these and other considerations it is apparent that K_α is associated with the rate of ionization, K_1, and that the gap between K_α and K_t is a measure of internal return.

Further consideration of Figure 3 makes it apparent that a two stage salt effect is being observed. At concentrations greater than 0.03 M lithium perchlorate, a typical normal salt effect is observed. At lower lithium perchlorate concentrations, a rapid increase in K_t is found with increasing salt concentration. The latter has been referred to by Winstein as the "special salt effect".[15] Other esters showing a similar two stage salt effect include p-anisylethyl p-toluenesulfonate,[15] trans-2-p-anisylcyclohexyl p-bromobenzenesulfonate,[15] cholesteryl p-toluenesulfonate[10] and erythro-3-p-anisyl-2-butyl p-bromobenzenesulfonate.[15] It is interesting to compare this list with a number of very similar compounds displaying only a normal salt effect. This list includes 1-phenylethyl p-toluenesulfonate,[15] cyclohexyl p-toluenesulfonate[17] and 3-phenyl-2-butyl p-toluenesulfonate.[17]

A study of the data obtained for special salt effects shows that $(\text{salt})_{1/2}$ -- defined as that concentration of salt at which $K_t - K_t^o = \frac{K_{ext}^o - K_t^o}{2}$ -- varies with changes in salt in the same order as in the normal salt effect: $LiClO_4 \cong HClO_4 > DPGHClO_4 > LiOAc$. On the other hand, the ratio K_{ext}^o/K_t^o is the same for all the salts used.[10]

One possible explanation for the special salt effect would be in terms of a salt-promoted ionization to give an ion quadruplet.[5] The special salt rate increase would then be due to the fraction of ion quadruplets which went on to give solvolysis product. The failure of K_α, the ionization rate, to show changes which are similar to those observed for K_t in the region of the special salt effect, indicates that the special salt effect is not involved in the ionization step.

It has already been stated that the normal salt effect acts through an ion atmosphere effect on the ionization rate. It is evident, however, that the special salt effect cannot be explained in terms of ion atmosphere reduction of return from II, III or IV. One characteristic of the previously described normal or ion atmosphere effect was the variation in its magnitude among different salts. The special salt effect, however, showing a constant K_{ext}^o/K_t^o, is independent of salt variations indicating that all salts eliminate

the same amount of return.[10] The common ion gives no special salt effect, although an ion atmosphere description would predict that it should. Finally, an ion atmosphere formulation cannot account for the previously mentioned absence of special salt effect in structures very similar to those which do show it.

From studies on threo-3-p-anisyl-2-butyl p-toluenesulfonate (XI) (for which there is a special salt effect and no common ion effect), it has been demonstrated that IV, the dissociated ion, is not formed.[13]

We are then left with the necessity to postulate a direct interaction between salt and ion pair. The result of this interaction is to produce species incapable of ion pair return, thus increasing K_t. This may be described as an exchange process between an ion pair and the salt (also probably an ion pair) to give a new ion pair capable only of solvolysis. The question remains as to whether II or III is undergoing exchange. It is apparent that the solvent-separated ion pair III would be more reactive to external salt. The fact that the special salt effect is capable only of partial reduction of ion pair return ($K_\alpha \neq K_t$) makes it obvious that it is primarily III which is being intercepted. The failure to observe special salt effects with systems similar to XII indicates that return from III is not important for them.[5]

Another example of exchange is found with XII. Comparison of its solvolysis rate in the presence of lithium p-toluenesulfonate with the rates for XI and XII in the absence of added salt (Figure 4) makes it obvious that during the reaction, XII is being converted to the slower reacting XI by exchange.[13]

For purposes of summary, it is interesting to compare XI, XII and 3-phenyl-2-butyl p-toluenesulfonate (XIV). This comparison is facilitated by the fact that for these compounds, dissociation is not taking place,[13] allowing simplification of the kinetic expression 4.[5]

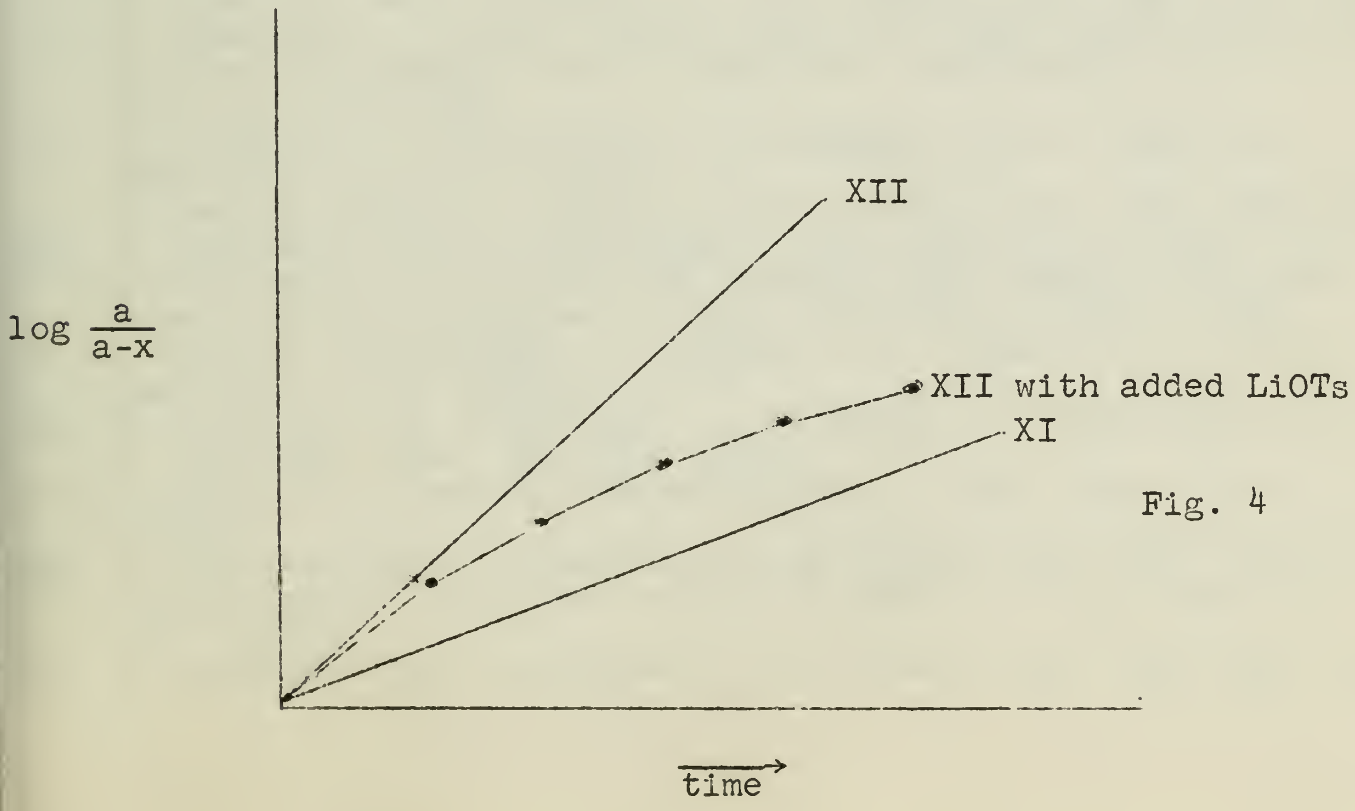


Fig. 4

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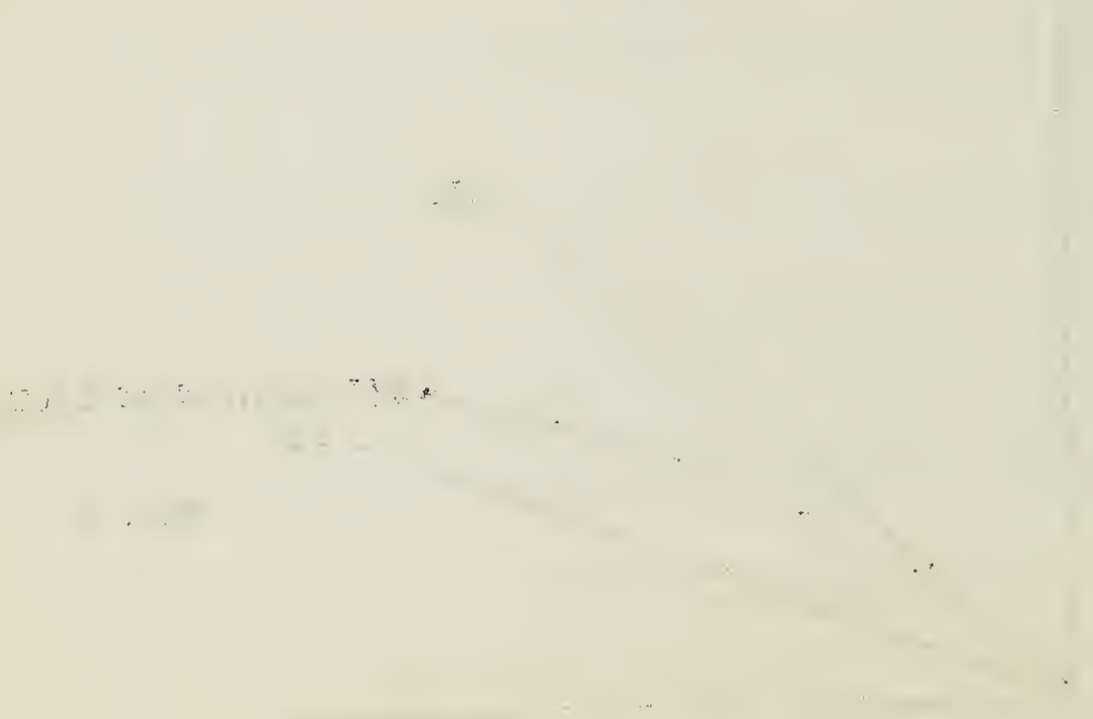

Using this, it is possible to obtain values for percentage ion pair return from II (equal to 100 $\frac{K_{-1}}{K_{-1}+K_2}$) and III (equal to 100 $\frac{K_{-2}}{K_{-2}+K_s^{III}}$) as well as total ion pair return (equal to 100 $\frac{K_\alpha^o - K_t^o}{K_\alpha^o}$).

Table IV[5]

Solvent	Compound	Temperature	% Ion pair return from II	% Ion pair return from III	total
HAc	XIV	50	78	0	78
	XI	25	38	83	78
	XII	25	37	81	75
EtOH	XIV	75	51	0	51
	XII	25	21	0	21

From Table IV it can be seen that increased stability of the carbonium ion, resulting from methoxy substitution or use of a less nucleophilic solvent, permits more return from III. In general, it can be said that the greater the stability of the carbonium ion, the further to the right in Scheme (1) the equilibrium will lie.

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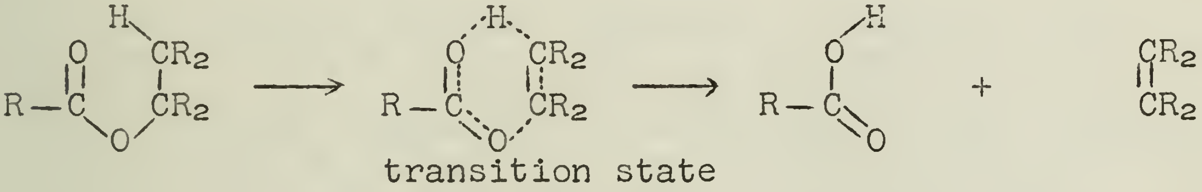
FACTORS CONTROLLING THE DIRECTION OF ELIMINATION IN THE PYROLYSES OF ESTERS OF ACETIC ACID

Reported by J. A. Kampmeier March 30, 1959

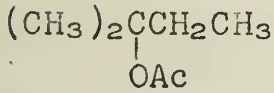
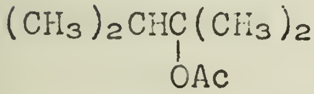
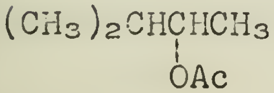
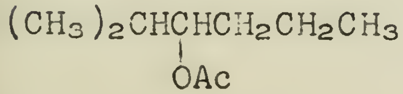
The gross aspects of olefin formation by means of ester pyrolysis have long been recognized. The apparent preference of the leaving groups for a cis-orientation, the unimolecular, homogenous nature of the decomposition, the negative entropy of activation, the lack of skeletally rearranged products and the absence of any effect by free radical inhibitors or initiators on the rate have been generally accepted as direct implications of a molecular transition state (1,2).



Recently, however, some of the more salient features of these elimination reactions have been examined. In particular, the direction of elimination in systems in which competing pathways are possible (i.e., acetates of secondary and tertiary alcohols) has been subjected to close scrutiny. Although the results of these investigations have been somewhat contradictory, it appears possible at present to obtain a fairly reasonable and cogent, although tentative, description of some of the factors controlling acetate pyrolyses.

Bailey (3,4) originally reported that acetate pyrolyses were highly selective with regard to the direction of elimination. In the series of aliphatic secondary and tertiary acetates investigated, more than 95% of the least alkylated olefin (Hofmann Rule) was claimed as product. None of the more stable olefin (Saytzeff Rule) was identified. The following data were presented at that time.

TABLE I

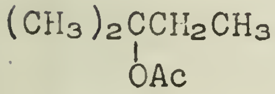
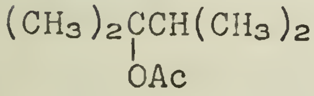
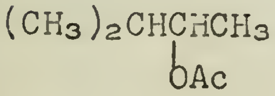
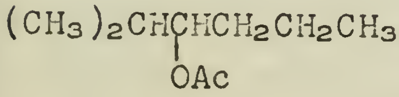
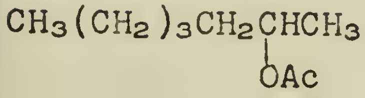
Ester	Temperature	% Hofmann Elimination	Analytical Method	Reference
 $(CH_3)_2\underset{\text{OAc}}{\underset{\vert}{C}}CH_2CH_3$	400°	>95	b.p., n_D	3
 $(CH_3)_2CH\underset{\text{OAc}}{\underset{\vert}{C}}(CH_3)_2$	400°	>98	b.p., n_D	3
 $(CH_3)_2CH\underset{\text{OAc}}{\underset{\vert}{C}}HCH_3$	500°	100	b.p., n_D, IR	4
$(CH_3)_2CHCH_2\underset{\text{OAc}}{\underset{\vert}{C}}HCH_3$	450°	>95	b.p., n_D	4
 $(CH_3)_2CH\underset{\text{OAc}}{\underset{\vert}{C}}HCH_2CH_2CH_3$	450°	>95	b.p., n_D	4

Since the conversion of ester to olefin was not complete, the term "% Hofmann Elimination" represents the amount of least alkylated olefin in the total olefin mixture. The pyrolyses were conducted at the temperatures indicated, in a nitrogen atmosphere, by dropping the liquid acetate through a vertical, heated column packed with Pyrex helices or beads. In a typical run, the resulting pyrolysate was extracted with water. Titration of an aliquot of the aqueous layer allowed calculation of the percent conversion of ester to acetic acid. The organic layer was fractionated through a 6"-helix packed column. Analysis of the distillate was performed as indicated in Table I. It had been previously demonstrated that carbon deposition on the column promoted isomerization of the resulting olefins (5). Accordingly, the flow rate and percent conversion of ester to olefin were adjusted in such a fashion as to prevent carbonization.

The apparent absolute obedience to Hofmann's rule in these cases led Bailey (4) and Maccoll (6) to speculate that the rate determining step in ester decomposition might involve a nucleophilic attack by the carbonyl oxygen on the β-hydrogen. Alkyl substitution at the β-carbon atom would increase the electron density at this atom and hence decrease the rate of attack by the nucleophilic oxygen atom. Accordingly, the rate of attack by oxygen would be greatest at the least alkylated β-carbon atom and the Hofmann rule would obtain. Similarly, statistical considerations of the numbers of available hydrogens indicate a preference for the formation of the least alkylated olefin. Bailey, however, correctly realized that neither of these rationalizations was sufficient to accommodate the almost absolute specificity observed (4).

The validity of Bailey's original claims are challenged by the more recent work of DePuy and colleagues (7) and Royals (8). The pyrolyses of a series of aliphatic and alicyclic acetates were performed under conditions apparently similar to those employed by Bailey (3,4). Bailey has also reinvestigated some of his previous results (9). All of the following product compositions were determined by means of vapor phase chromatographic analysis. The term "% calculated Hofmann elimination" is based upon the numbers of available hydrogen atoms.

TABLE II

Ester	Temperature	% Hofmann Elimination	% Calculated Hofmann Elimination	Reference
 $(CH_3)_2\underset{OAc}{\underset{\mid}{C}}CH_2CH_3$	400°	76	75	7
	400°	74	75	9
 $(CH_3)_2\underset{OAc}{\underset{\mid}{C}}CH(CH_3)_2$	400°	88	86	9
 $(CH_3)_2CH\underset{OAc}{\underset{\mid}{C}}HCH_3$	450°	80	75	7
 $(CH_3)_2CH\underset{OAc}{\underset{\mid}{C}}HCH_2CH_2CH_3$	450°	73	67	7
 $CH_3(CH_2)_3CH_2\underset{OAc}{\underset{\mid}{C}}HCH_3$	485°	54	60	8

In contrast to Bailey's original findings, these latter data indicate that the direction of elimination is almost random; i.e., the relative amounts of products formed are in close agreement with those predicted by a statistical consideration of the numbers of available hydrogen atoms.

With regard to the examples presented in Tables I and II, it seems most reasonable to attribute the contradictions to the inadequacies of boiling point and index of refraction as criteria of purity and identity. As was previously noted, in only one case was even qualitative infrared analysis of the olefin mixture reported. Vapor phase chromatography, on the other hand, has repeatedly been found to be a reliable method for the fractionation of complex mixtures. When standardized retention times are considered, the method further affords an indication of the identity of the component fractions (10).

DePuy has established that neither positional nor geometrical isomerization of the product olefins under the conditions of the reaction is likely (7). Thus, n-butyl acetate was pyrolyzed in the presence of cis-butene. The only products obtained were cis-butene and 1-butene. In several cases the pyrolysate was recycled without any changes in the olefin composition. Furthermore, the pyrolyses of several primary acetates produced only the corresponding terminal olefins. Bailey and DePuy disagree at the present time with respect to the effect of temperature on the course of the elimination (7,9, 11). Discrepancies also exist with regard to the effects of other experimental variables. The following data for the pyrolysis of 1-methylcyclohexyl acetate are relevant.

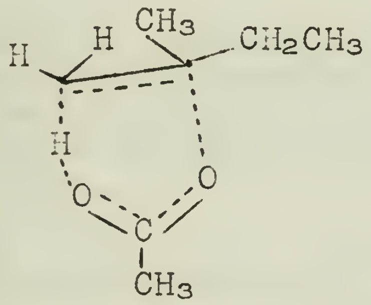
TABLE III

Packing	Temperature	% Endo Isomer	Remarks	Reference
Desicote on helices	350°	76		7
NaOH on helices	450	82	Charring	7
H_2SO_4 on helices	450	99	Charring	7
Acid-treated silica	350	99		7
Helices	350	72		7
Helices	400	73		11
Helices	450	74		7
Helices	550	74		7
Helices	220	83	Liquid Phase	9
Helices	300	85		9
Helices	400	82		9
Helices	450	74		9
Helices	550	74		9

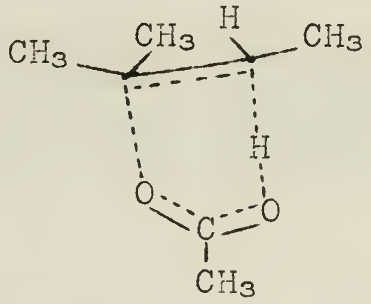
DePuy (7) has found only a slight variation in the olefin ratio produced by the pyrolysis of 1-methylcyclohexyl acetate from 350°-550°. Bailey, on the other hand, reports a variation in the endo/exo ratio from 85/15 to 74/26 through the range 300°-550°. A similar disagreement is found with respect to the pyrolysis of t-amyl acetate. DePuy has reported that the pyrolysis at 350°, 400° and 500° gives olefin ratios consistent to within three percent. At 250°, no detectable amounts of olefin were formed (11). Bailey reports that the same pyrolysis at 225° gives an olefin mixture consisting of 58% of 2-methyl-2-butene and 42% of 2-methyl-1-butene.

This ratio changes progressively as the temperature is increased; at 400°, 74% of the mixture is 2-methyl-1-butene. Similar anomalies are apparent with respect to the effect of acid on the direction of elimination. As noted in Table III, DePuy has found only the more stable 1-methylcyclohexene when the column was pre-treated with a strong acid. Bailey, however, states that in the same pyrolysis, the effects of acidic or basic treatment of the column were negligible. Essentially identical results were also obtained when the ester was diluted with 5% pyridine or excess acetic acid. Complete solutions to the problems raised by these discrepant results may require further experimentation. Both authors have confirmed the fact that the column is not affected by the pyrolysis. DePuy has collected fractions of the pyrolysate (7) and Bailey has performed consecutive pyrolyses through the same tube (9). The olefin ratios were identical in both cases. Free radical inhibitors or initiators did not effect the reaction (9).

These contradictions with respect to temperature and acid catalysis notwithstanding, certain comments concerning the direction of elimination in aliphatic compounds are possible. The random nature of the elimination process is evidenced by the data in Table II. Such a finding might seem to indicate that the effects of steric and electronic factors are rather evenly balanced. For example, the pyrolysis of t-amyl acetate at 400° gives a 76% yield of the corresponding 1-olefin (7). Statistically, a 75% yield of the terminal olefin would be anticipated. A priori, this close agreement might not have been expected. The transition states for the formation of the two olefins are probably as follows.



Transition state for the
formation of 1-olefin



Transition state for the
formation of 2-olefin

Steric considerations of the methyl-methyl interaction in the transition state for the formation of 2-olefin would seem to favor the formation of 2-methyl-1-butene. However, the transition state from the formation of 2-olefin should be preferred in terms of the greater stability of the incipient olefin. Since the observed distribution is random, these opposing effects would appear to be of approximately equal magnitude. In a similar fashion, the olefin distribution obtained from the pyrolysis of sec-butyl acetate may be rationalized. Fifty-seven percent of 1-butene, 28% trans-butene and 15% cis-butene were found to be present (7). A comparison of the transition states involved is again fruitful. If the process were completely random, the anticipated isomer distribution would be 60% 1-butene, 20% trans-butene and 20% cis-butene. Although the distribution between 1- and 2-butene is very close to that predicted, the relative amounts of cis- and trans-butene deviate considerably. The difference may be quite reasonable in terms of the unfavorable

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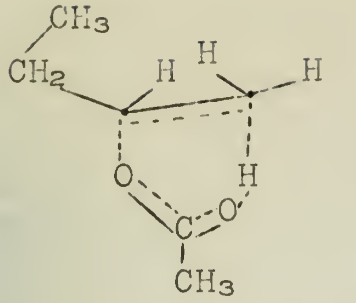
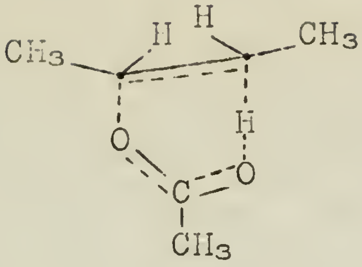
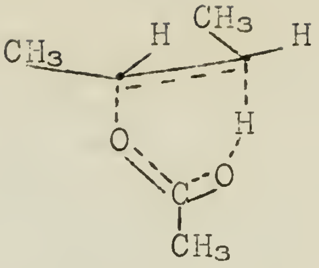


Transition state
for the formation
of 1-butene



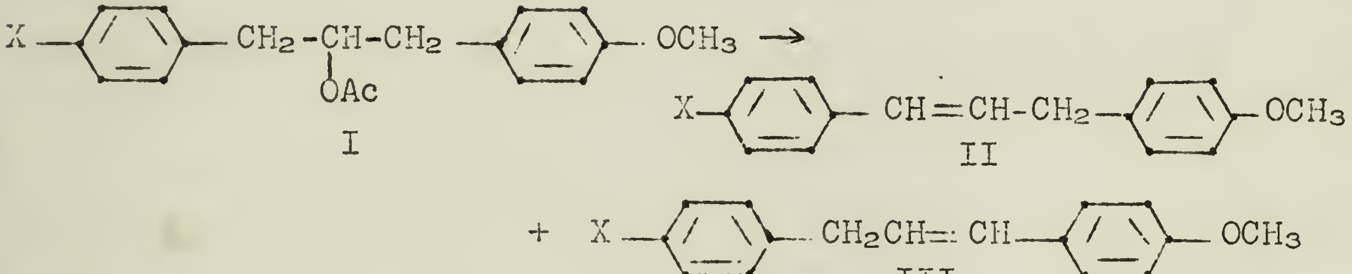
Transition state
for the formation
of trans-butene



Transition state
for the formation
of cis-butene

methyl-methyl interaction in the transition state leading to _cis_-butene. Curtin and Kellom have observed the same type of effect in the preferential formation of _trans_-stilbene from the pyrolysis of the _erythro_- and _threo_-2-deutero-1,2-diphenylethyl acetates (12). Similarly, somewhat more _trans_-butene is obtained than predicted. Such a result may again be attributed to the greater stability of _trans_-butene with respect to 1-butene (13). To the extent that the transition states have any olefinic character, this difference in olefin stability should be reflected in the olefin ratios. Royals (8) has observed a similar isomer distribution in the pyrolyses of the 2- and 3-heptyl acetates. In conclusion, then, it seems as if small steric and electronic effects may be operative in the pyrolyses of simple aliphatic acetates, but that such factors are relatively unimportant. As a result, the elimination occurs in an approximately random fashion.

DePuy has investigated an elegantly designed case in which only electronic effects may operate (14). The isomer distributions from the thermal decompositions of 1,3-diaryl-2-propyl acetates were studied as a function of the substituents in the _p_-position of the phenyl rings.



I

II

III

The pyrolysis of 1-phenyl-3-_p_-methoxyphenyl-2-propyl acetate (I, X=H) produced a mixture of the two possible olefins consisting of 73% of the olefin conjugated with the ring containing the methoxyl function (III, X=H). It was previously reported (15) that basic equilibration of a mixture of the two possible olefins resulted in 70% of the olefin conjugated to the _p_-anisyl group (III, X=H). Similarly, the pyrolysis of 1-(_p_-chlorophenyl)-3-(_p_-methoxyphenyl)-2-propyl acetate (I, X=Cl) produced 84% of the olefin conjugated with the anisyl function (III, X=Cl). Equilibration of a mixture of the isomers (14) with sodium in ethanol produced a mixture containing 85% of this same olefin (III, X=Cl). Control experiments were performed to demonstrate that olefin equilibration did not occur under the conditions of the thermal decomposition. The analytical procedure was based upon a differential solvolysis of the bromides formed by reaction of the

olefins with hydrobromic acid. This procedure was standardized and found to be accurate to within 3%. The possibility of an E_1-type elimination was discounted by the small differences in the rates of thermal elimination of acetic acid from 1-*p*-methoxyphenyl-3-phenyl-1-propyl acetate and 1-phenyl-3-*p*-methoxyphenyl-1-propyl acetate. Since neither steric nor statistical phenomena are relevant in these cases, any deviation in the olefin ratio from unity should probably be attributed to an electronic effect. The essential identity of the olefin ratio obtained from the pyrolysis and that found by equilibration studies implies that the stability of the resulting olefin determines the rate of ester decomposition. Accordingly, the transition state may be pictured as involving a well-developed double bond. The resonance interactions with the aryl groups which determine the final olefin stability are similarly operative in the transition state.

Bailey has considered the pyrolyses of a number of substituted aliphatic acetates (16,17). His data, as well as others available in the literature are summarized below.

TABLE IV

Ester	% Acetic Acid Liberated	Products: % Yield		Reference
$\phi CH_2\underset{OAc}{CH}CH_3$	56	$\phi CH=CHCH_3$ $\phi CH_2CH=CH_2$	40 13	17
$(C_6H_5)_2CH\underset{OAc}{CH}CH_3$	83	$(C_6H_5)_2C=CHCH_3$	71	17
$CH_3\underset{OAc}{CH}CH_2CO_2Et$	60	$CH_3CH=CHCO_2Et$	56	17
$CH_3\underset{OAc}{CH}CH_2NO_2$	--	$CH_3CH=CH-NO_2$	85	18
$CH_3\underset{OAc}{C}(C_2H_5)CN$	83	$CH_2=\underset{C_2H_5}{C}-CN$	73	19
	--	$CH_2=\underset{C_2H_5}{C}-CN$ $+\ CH_3\underset{\underset{CHCH_3}{\Vert}}{C}-CN$	-- --	20
$CH_3\overset{\phi}{C}H\overset{OAc}{C}HCH_3$	--	$\phi\overset{CH_3}{C}=CHCH_3$	cis 38 trans 31	21
$CH_3OCH_2\underset{OAc}{CH}CH_3$	58	$CH_3OCH_2CH=CH_2$	48	16
	57	$CH_3OCH_2CH=CH_2$ $CH_3OCH=CHCH_2$	27 cis 13 trans 18	11

A portion of these data was interpreted by Bailey as evidence that the more acidic hydrogen was preferentially removed (16,17). This argument was invoked earlier to account for the formation of the

least alkylated olefin in the pyrolyses of unsubstituted aliphatic acetates. It was originally reported (16) that the pyrolysis of 1-methoxy-2-propyl acetate produced exclusively methyl allyl ether. This case has been experimentally re-examined by DePuy (11) with the aid of vapor phase chromatographic analysis. The major product, contrary to Bailey's original report, is 1-methoxypropene. The pyrolysis of 1-cyano-1-methylpropyl acetate remains somewhat controversial. It seems quite probable that a re-evaluation of this case will vindicate the claim of Chapin and Smith (20) that a mixture of the two possible olefins is formed.

Were the acidities of the β-hydrogens important in determining the direction of elimination, the observed olefin ratios in the decomposition of 1,3-diarylpropyl acetates would be inexplicable. A consideration of Hammett's σ_p constants (22) for the three substituents examined (p-OCH_3, -0.268; p-H, 0.0; p-Cl, + 0.227) predicts that the hydrogens adjacent to the anisyl ring are least acidic, those adjacent to the phenyl ring intermediate and those adjacent to the p-chlorophenyl ring most acidic. The olefin distribution should follow in the same order if hydrogen acidity is determinate. DePuy has, in fact, observed the inverse order. As was concluded previously, the olefin ratio is best understood in terms of olefin stability. This concept of olefin stability is completely compatible with the data in Table IV and is similarly supported by a recent report by Benkeser and Hazdra (24). DePuy (11) is of the opinion that in cases involving strongly electron attracting substituents (i.e., $>C=O$, $-NO_2$), the acidity of the hydrogens may be important. In these cases, the mechanism of the reaction may actually involve an intermediate carbanion and trans-elimination. Such a case involving the pyrolysis of a xanthate ester has recently been identified by Bordwell and Landis (23).

Some of the most confusing work in the field of acetate pyrolyses deals with various alicyclic esters. A portion of the available data has already been considered with regard to the effect of experimental conditions on the distribution of the isomeric, olefinic products. The remaining data concerning the thermal decomposition of 1-methylcyclohexyl acetate are tabulated below.

TABLE V

	Products		
Temperature	% exo	% endo	Reference
450°	100	0	3
450	86	14	25
450	83	?	26
450	26	74	7,9
430	22	78	27

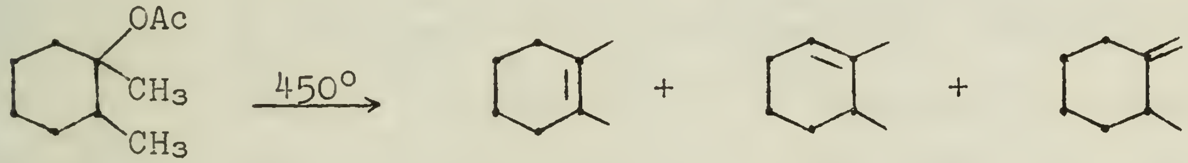
Bailey's original report claimed, in agreement with his results in the acyclic field, that the pyrolysis of 1-methylcyclohexyl acetate afforded only the least substituted olefin, methylenecyclohexane. The analytical method employed suffered from the same deficiencies mentioned earlier. The fact that Bailey's original results were apparently confirmed by independant investigators (25,26) makes possible the existence of an abnormal, undefined set of experimental conditions leading to a predominance of the least substituted olefin. A detailed examination of these apparent confirmations is relevant.

Bailey has now prepared authentic samples of 1-methylcyclohexene and methylenecyclohexane (9). These isomers were found to be at least 99% pure by vapor phase chromatographic analysis. This pure sample of methylenecyclohexane does not contain infrared absorption bands at either 833 or 1110 wave numbers. Hammond and Nevitt (25) reported, in agreement with Bailey, that the thermal decomposition of 1-methylcyclohexyl acetate yields predominantly the exo-isomer. Their isomer distributions were obtained by means of a graphical interpolation from the infrared spectra of control mixtures to the spectra of the pyrolysate. Absorption bands at 1110, 981 and 833 wave numbers were employed to calculate the percent methylenecyclohexane present. Since two of these bands are apparently absent in pure methylenecyclohexane, it would seem as if Hammond's standard samples were actually mixtures. Traynham and Pascual (26) have offered work which has been quoted as confirmation on the belief that the exo-isomer is preferentially formed (9). In their hands, the pyrolysis afforded, after fractionation, a product in 83% yield (based on ester consumed), b.p., 108-109°. This product was reported to be methylenecyclohexane. Pure 1-methylcyclohexene, according to Bailey (9), boils at 109.7-110°. A boiling point of 103° is usually quoted for methylenecyclohexane (28). Traynham and Pascual found only slight differences in the infrared spectra of the two isomers, whereas both Bailey and DePuy report that the spectra of the pure isomers are quite different. The most convincing evidence offered by Traynham and Pascual involves the formation of derivatives. Thus the olefin was converted to a glycol in 43% yield (based on ester). The glycol, on treatment with concentrated hydrobromic acid gave a 35% overall yield of cyclohexanecarboxyaldehyde. The only logical conclusion, based on these data, is that, barring unusual rearrangements or side reactions in the conversion of olefin to aldehyde, the original olefin must have contained at least 35% of methylenecyclohexane. This value of 35% is not greatly in disagreement with the results obtained by the use of vapor phase chromatography (7,9). The more recent data offered by DePuy (7) and Bailey (9) indicate that the pyrolysis of 1-methylcyclohexyl acetate gives 74% of 1-methylcyclohexene and 26% methylenecyclohexane. Such a ratio is concordant with data obtained by vapor phase chromatographic, nuclear magnetic resonance and infrared analytical methods. Although the existence of an abnormal set of reaction conditions is always possible, it seems more reasonable to attribute the earlier results to an inadequate analytical scheme.

Several other secondary and tertiary alicyclic acetates have been pyrolyzed. Only data considered to be analytically sound will be discussed. Conflicting data are, as usual, available in the literature (25,26,29). In the simplest alicyclic cases, the pyrolyses of the 1-methycycloalkyl acetates , the products consist predominantly of the endocyclic olefins (30). Thus, 1-methylcyclopentyl acetate gives an endo/exo ratio of approximately 86/14 (7,31). The corresponding cycloheptyl case affords a ratio of 76/24. Statistically, these isomer distributions would not have been expected. It has been noted (7, footnote 19) that because of the difference between a freely rotating methyl group and the relatively rigid cis-ring hydrogens, the ratio of available exo-hydrogens to endo-hydrogens, at any given time, might be close to unity. It is probable that the observed preferential formation of endo-isomer is due in part to the greater stability of this olefin. In the cyclopentyl, cyclohexyl

and cycloheptyl series, the heats of hydrogenation of the exo-isomers are 2-4 kcal/mole greater than those for the endo-olefins (32). Similarly, formation of the transition state leading to exo-olefin involves the loss of the free rotation of the methyl group. This unfavorably entropy term is not encountered when the transition state involves the more rigid ring hydrogens.

The pyrolysis of trans-2-phenylcyclohexyl acetate, in which elimination may proceed to afford either conjugated or non-conjugated olefin, gave 86% of the conjugated 1-phenylcyclohexene. The remainder of the product was the non-conjugated 3-phenylcyclohexene (33). These results are in accord with those quoted earlier concerning the pyrolysis of 1-phenyl-2-propyl acetate (cf. Table IV). Finally, the cis- and trans-isomers of 1,2-dimethylcyclohexyl acetate have been studied (7).



cis	28%	26%	56%
trans	0%	45%	55%

The lack of formation of 1,2-dimethylcyclohexene from the trans-isomer is indicative of the general steric requirements of the elimination (1,2). More interesting, however, is the ratio of the olefins formed. Since there is only one ring hydrogen available for reaction, as opposed to approximately two methyl hydrogens, a predominance of the exo-olefin might be anticipated. This factor, however, must be balanced against the greater enthalpy of the incipient exo-isomer and the unfavorable entropy term involved in the formation of exo-product. The product ratios suggest that these factors are rather evenly balanced. The data concerning the thermal decomposition of cis-1,2-dimethylcyclohexyl acetate are somewhat reminiscent of those obtained in simple aliphatic cases; the product distribution is seemingly random. In this case, the factors favoring the formation of endo-olefin should still be operative. However, the formation of the exo-isomer may involve the relief of considerable steric strain due to the cis-1,2-dimethyl interactions in the parent acetate.

In conclusion, it seems as if two separate cases must be considered. In the first category are those acetates containing substituents capable of resonance interaction with the incipient olefin on one or both of the β-carbon atoms. In such cases, the transition state for the elimination will resemble olefin and accordingly, the most stable(conjugated) product will be preferentially formed. In the more complicated case of simple aliphatic or alicyclic acetates, an ex post facto rationalization of the product ratios seems to be representative of the limit of our present understanding.

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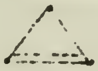
THE CHEMISTRY OF CYCLOPROPENE AND ITS DERIVATIVES

Reported by N. D. Werner

April 6, 1959

INTRODUCTION

This report will cover the chemistry of cyclopropene (I) and the derivatives of cyclopropene of established structure. Cyclopropene is of interest because of its bearing on the effect of ring strain and bond hybridization. Some of the derivatives of cyclopropene, such as the cyclopropenyl cation (II) (1) and diphenylcyclopropenone (III) (2), are of interest because these compounds test the molecular orbital theory as delineated by Hückel (3), which states simply that of the conjugated monocyclic polyolefins, only those which have $4n+2$ π-electrons ($n=0,1,2---$) will be especially stable because of electron delocalization. Since both the cyclopropenyl cation and diphenylcyclopropenone are monocyclic conjugated olefins with two π-electrons ($n=0$) they should be aromatic.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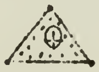
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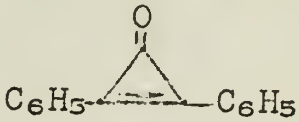
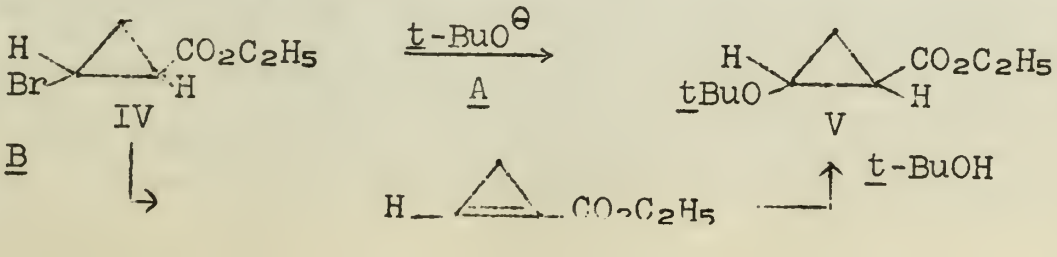


III

ACETYLENIC CHARACTER OF THE CYCLOPROPENE MOLECULE

Cyclopropane exhibits many properties which are characteristic of olefins. It reacts with bromine to yield 1,3-dibromopropane and is also attacked by hydrobromic acid to yield propyl bromide (4). From spectroscopic evidence it seems that cyclopropane can conjugate with unsaturated groups. Coulson and Moffitt (5), as well as Walsh (6), have proposed models for cyclopropane which account for many of these olefinic properties. Walsh pictures cyclopropane as consisting of an equilateral triangle with three 2p-orbitals overlapping in the plane of the ring outside of the equilateral triangle. Each carbon atom also has an sp^2-orbital which is directed to the middle of the triangle. In the cyclopropane molecule as described by Coulson and Moffitt the carbon atoms are bonded together by sp^3-hybridized orbitals which are not directed at each other, but are "bent" and are outside the triangle. If a double bond is introduced into these models for cyclopropane it would appear that some acetylenic character would be developed in the cyclopropene molecule. In a series of experiments Wiberg and coworkers (7) have established that cyclopropene does possess acetylenic character.

In trying to synthesize cyclopropenecarboxylic acid by elimination of hydrogen bromide from ethyl 2-bromocyclopropanecarboxylate (IV) with potassium t-butoxide, ethyl 2-t-butoxycyclopropanecarboxylate (V) was isolated. Two routes appear possible for the formation of the saturated ether-ester. One process would involve a nucleophilic attack on the 2-carbon by t-butoxide ion. The other process would involve elimination of hydrogen bromide followed by Michael addition of t-butyl alcohol.



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It was noted that the bromide in IV was quite inert to treatment with sodium iodide in acetone and alcoholic silver nitrate. This experimental evidence would seem to rule out a direct nucleophilic attack as postulated by path A. In order to determine which reaction path was the real one the reaction was repeated, but the solvent was now t-butyl alcohol-d. Path A would lead to the introduction of at most a small amount of deuterium while path B would require the introduction of one deuterium atom per molecule. The mass spectrum of the product using the deuterated solvent indicated the presence of two deuterium atoms per molecule.

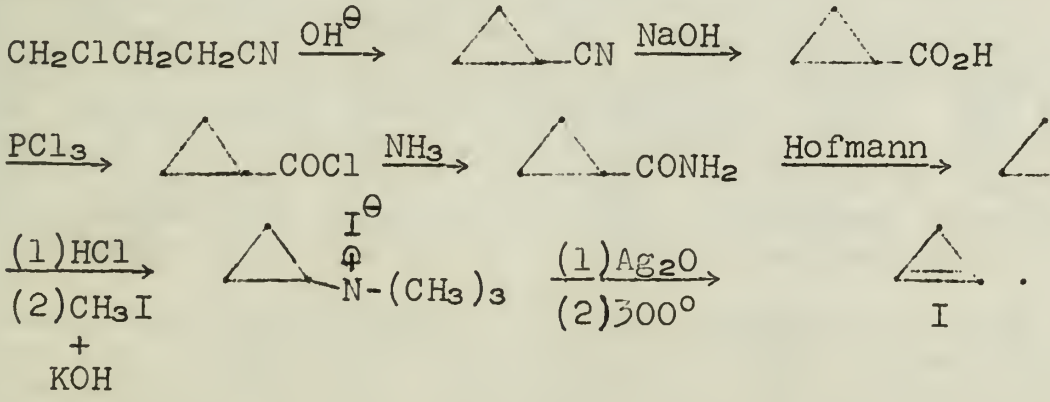
The reaction course represented by path B would certainly indicate that one of the deuterium atoms is at the 1-position. It seems plausible that the other deuterium atom is at the 2-position since one would expect both hydrogens of the 3-position to exchange, which would lead to the incorporation of four atoms of deuterium per molecule. The deuterated ester was hydrolyzed to a β-formylpropionic ester (VI). The nuclear magnetic resonance spectrum of VI indicates that the deuterium atom is in the aldehyde group, which indicates in turn that the second deuterium atom is in the 2-position of the deuterated cyclopropane ester.

A reasonable course for the conversion of IV to V would involve elimination of hydrogen bromide followed by exchange of the vinyl hydrogen with solvent and then Michael addition of t-butyl alcohol. These results confirm the predicted acetylenic character of cyclopropene.

CYCLOPROPENE

In 1893 Freundler (8) reported the preparation of cyclopropene by the dry distillation of a mixture of calcium and barium furoates with soda lime. Cyclopropene itself was not isolated, but the gaseous mixture from the pyrolysis was passed into bromine and dibromocyclopropane was reported as one of the products isolated. Hurd and Pilgrim (9) tried to confirm the results obtained by Freundler, but could only isolate furan and small amounts of propyne.

Demyanov and Dojarenko (10) prepared cyclopropene in the following manner:

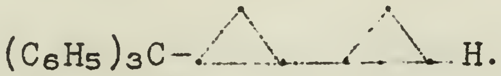


The trimethylcyclopropyl ammonium hydroxide was introduced dropwise into a quartz flask containing a few pieces of platinized clay. Since the cyclopropene obtained decomposed readily, the elimination was carried out in an atmosphere of carbon dioxide and away from direct light. Upon treatment of I with bromine 1,2-dibromocyclopropane was obtained. It was also reported that I could be obtained by treatment

of the dibromo compound with zinc dust in alcohol.

Schlatter (11) prepared cyclopropene in a manner quite similar to that of Demyanov and Dojarenko. He reported however that he could not regenerate I upon treatment of the dibromo compound with zinc dust and alcohol. Cyclopropane was the major product isolated from the debromination reaction.

The Diels-Alder adduct of cycloheptatriene and diethyl acetylenedicarboxylate (12) upon heating gives diethyl phthalate, a small amount of cyclopropene (0.5%), and a substance which appears to be polycyclopropene. Cyclopropene itself polymerizes readily at room temperature without a catalyst (12) to give a material which is indicated to be polycyclopropene from its infrared and nuclear magnetic resonance spectra. Cyclopropene is also polymerized by bases (12). It reacts with sodium triphenylmethide and triphenylboron to give a salt. The hydrolysis of the salt gives a series of compounds which are composed of one triphenylmethane and n cyclopropenes. The main component is:



Passage of cyclopropene over aluminum oxide at 245-255° and 345-355° gives a liquid with the empirical formula C_3H_4, which appears to be a polymer of cyclopropene (13).

Cyclopropene upon treatment with potassium permanganate yields a mixture of products, one of which is formic acid (13). Wiberg (14) reports that cyclopropene is reduced by reagents such as chromium (II) chloride and the zinc-copper couple, but has not defined the reduction products. These reagents normally reduce alkynes to alkenes, but do not reduce alkenes. A complex is formed with silver ion which reacts further to give propionaldehyde (14). Cyclopropene reacts with ethyl diazoacetate to give a six-membered ring heterocycle, the reaction involving addition to the double bond and opening of the three-membered ring (12).

The microwave spectrum of cyclopropene has been examined by Kasai, Myers, Eggers and Wiberg (15). The carbon-carbon single bond distance is 1.515 Å and the carbon-carbon double bond distance is 1.300 Å . The carbon-hydrogen methylene bond distance is 1.087 Å and the vinyl carbon-hydrogen bond distance is 1.070 Å . The bond angles observed are 114°42' for the methylene hydrogen-carbon-hydrogen angle, 50°48' for the methylene carbon-carbon angle and 149°55' for the carbon-carbon double bond-hydrogen angle. The molecular structure of cyclopropene was also investigated by the method of electron diffraction (16). The values observed by the electron diffraction method were similar to those determined from the microwave spectrum except that there was a larger uncertainty in the values.

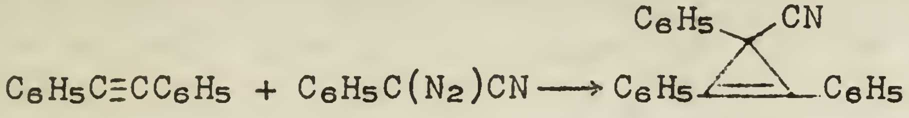
Deuterated cyclopropene (15) was prepared by using deuterium oxide as the solvent for the pyrolysis of the trimethylcyclopropyl ammonium salt. From the intensities of the microwave lines of the deuterated sample it was concluded that the deuterium was nearly randomly distributed between the vinyl and the methylene groups.

THE SYM-TRIPHENYLCYCLOPROPENYL CATION

Simple LCAO calculations predict that the cyclopropenyl cation
(II) should be aromatic. The calculated delocalization energy for

the cyclopropenyl cation is 2.00β(1) while the value for benzene is also 2.00β(17). Substantiating this hypothesis Breslow and Yuan (18) synthesized the *sym*-triphenylcyclopropenyl cation and determined some of its properties.

1,2,3-Triphenylcyclopropenyl cyanide (VII) was prepared by the reaction of diphenylacetylene with phenyldiazoacetonitrile. The



VII

cyanide is covalent, as silver cyanide is not precipitated upon the addition of alcoholic silver nitrate and VII is not soluble in polar solvents. The nuclear magnetic resonance spectrum rules out the possibility of a cyanide ion bound to a tight *sym*-triphenylcyclopropenyl cation since it indicates that two types of phenyl groups are present in the ratio of 2:1.

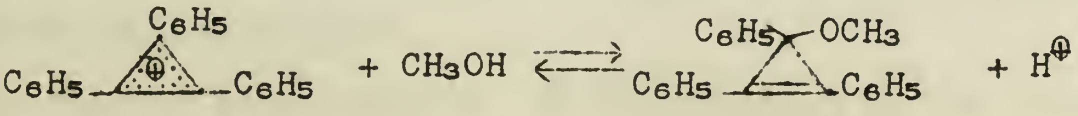
Upon treatment of the covalent cyanide with boron trifluoride etherate containing some water, a white, high-melting solid is obtained which is apparently a mixed fluoroborate-hydroxyfluoroborate of the *sym*-triphenylcyclopropenyl cation. The mixed fluoroborate-hydroxyflouroborate is insoluble in the usual non-polar organic solvents, but is soluble in methanol and ethanol. The nuclear magnetic resonance spectrum indicates the presence of only one type of phenyl group. The cyanide is regenerated upon mild treatment of the mixed fluoroborate-hydroxyflouroborate with potassium cyanide, indicating that the carbon skeleton has not undergone rearrangement. 1,2,3-Triphenylcyclopropene methyl ether (VIII) is formed upon treatment of the mixed fluoroborate-hydroxyfluoroborate with methyl alcohol. Aqueous alkali reacts with the cation to form the higher melting isomer of the two benzylidene desoxybenzoins (IX)(19).

$$C_6H_5CH{=}C(C_6H_5)COC_6H_5$$

IX

Salts of the *sym*-triphenylcyclopropenyl cation can be generated readily by treatment of the methyl ether with acid. *sym*-Triphenylcyclopropenyl bromide has been prepared in this manner. This bromide, in contrast to triphenylmethyl bromide, is ionic. This fact is evidence that the triphenylcyclopropenyl cation has a large electron delocalization energy associated with it, for both the triphenylcyclopropenyl cation and the triphenylmethyl cation can delocalize the positive charge in three benzene rings.

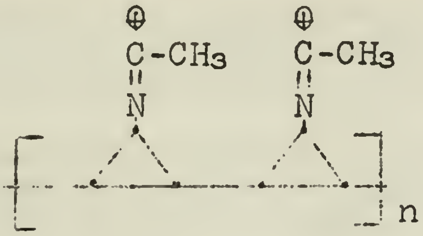
The *sym*-triphenylcyclopropenyl cation and the covalent derivatives have different ultraviolet spectra. Although the absorption occurs in the same regions, 310mμ and 330mμ, the cation absorption is at much higher intensity. Either the cation or the ether will be present in alcoholic solution depending upon the hydrogen ion concentration of the solution. In ethanol the transition occurs at a 1*N* acid concentration, while in acetonitrile-ethanol (9:1) the transition occurs at an acid concentration of 10^{-4}*N*. In contrast to



VIII

this behavoir the triphenylmethyl ether shows no cation formation even at much greater acid concentrations. This experimental evidence is another indication of the greater stability of the sym-triphenylcyclopropenyl cation as compared to the triphenylmethyl cation.

Wiberg (12) reports that cyclopropene reacts with trityl salts in acetonitrile in a hydride transfer reaction. The ion thus derived from cyclopropene then reacts with solvent, and appears to polymerize during the work-up. The formula postulated for the polymerized product is:



When other solvents are used the hydride transfer still occurs, but only intractable, polymeric materials result besides triphenylmethane.

It has not yet been determined how much of the stability of the cation is due to the cyclopropenyl aromatic structure and how much to the contribution of the phenyl groups. There is enough experimental evidence, however, to indicate that the LCAO calculation predicting aromaticity for the cyclopropenyl cation is qualitatively correct.

THE CYCLOPROPENYL ANION

Molecular orbital calculations (1) indicate that the cyclopropenyl anion, in contrast to the cyclopropenyl cation, should not be aromatic. However the molecular orbital theory predicts that certain substituted cyclopropenyl anions should have some extra stabilization due to electron delocalization. Such an anion would be the one derived from a 1,2-diphenylcyclopropene-3-carboxylic ester.

Breslow and Battiste (20) synthesized 1,2-diphenylcyclopropene-3-carboxylic acid from the reaction of diphenylacetylene and ethyl diazoacetate followed by hydrolysis. The acid was converted to the t-butyl ester by methylation and ester exchange. The t-butyl ester was refluxed with potassium t-butoxide in t-butyl alcohol-d(7) for 31 hours. The ester which was recovered contained 5% deuterium. After refluxing the ester for 57 hours the recovered ester contained 9.4% deuterium. Vigorous oxidation of the deutero ester with potassium permanganate indicated that the deuterium was incorporated in the cyclopropene ring, since the benzoic acid which was isolated from the reaction mixture contained no deuterium.

The authors concluded from this experimental evidence that the exchange reaction proceeds through a cyclopropenyl anion intermediate. The possibility of addition of alcohol to the double bond, exchange of the resulting cyclopropane, and subsequent elimination of the alcohol again was ruled out by an experiment in which the methyl ester of 1,2-diphenyl-2-methoxycyclopropanecarboxylic acid was recovered unchanged after refluxing with potassium t-butoxide for 67 hours.

DIPHENYLCYCLOPROPENONE

Diphenylcyclopropenone (2) was prepared by the reaction of benzal

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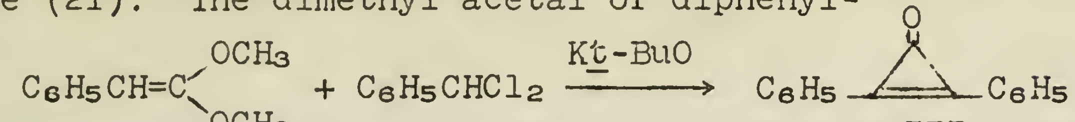
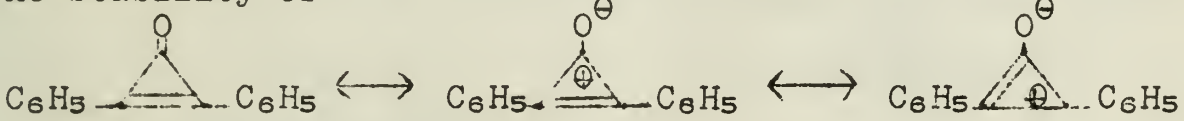
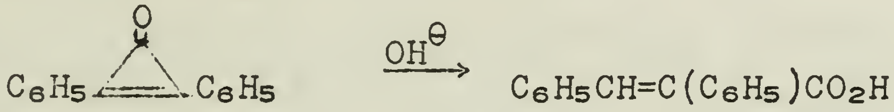
chloride, potassium t-butoxide and the dimethylacetal of phenyl ketene (21). The dimethyl acetal of diphenylcyclopropenone was not isolated since it is hydrolyzable on neutral aqueous treatment.


III

The melting of diphenylcyclopropenone at 121° is reversible, but if the melt is heated at 130-140° carbon monoxide is evolved (22). Diphenylacetylene is also isolated from the decomposition products.

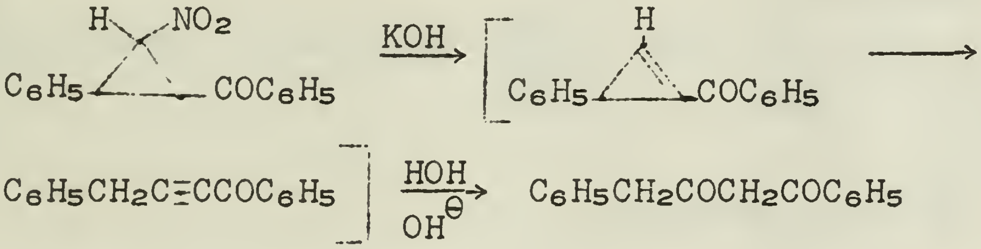
Cyclopropenone should be aromatic, because it is the analog in the two π-electron system of tropone in the six π-electron system. Resonance structures such as those indicated should contribute greatly to the stability of diphenylcyclopropenone. The fact that the cyclopropenone can be isolated from hydroxylic medium and that it decomposes at a relatively high temperature indicate that diphenylcyclopropenone must have large resonance stability to compensate for the high angle strain of the molecule. A simple LCAO calculation gives a vertical resonance energy of 1.4β. Diphenylcyclopropenone when treated with hydroxide ion rearranges to α-phenylcinnamic acid (X)(23).

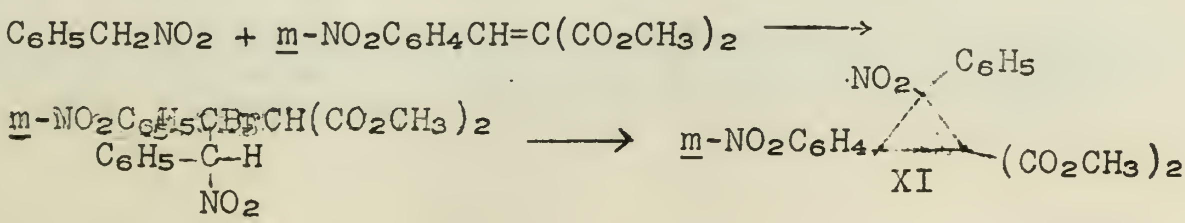



III X

SUBSTITUTED CYCLOPROPENE DERIVATIVES

Kohler and Smith (24) postulated a cyclopropene intermediate in the conversion of phenylbenzoylnitrocyclopropane with potassium hydroxide to an open chain β-diketone. In order to determine whether or not nitrous acid can actually be eliminated from a nitrocyclopropane Kohler and Darling (25) synthesized dimethyl 1-phenyl-1-nitro-2-(3'-nitrophenyl)-cyclopropanedicarboxylate (XI). Upon treatment of XI with sodium methoxide, dimethyl 1-phenyl-2-(3'-nitrophenyl)-cyclopropenedicarboxylate (XII) was obtained. Compound XII was hydrolyzed to give the dicarboxylic




XI

[illegible]

$$[illegible]$$

[illegible]

[illegible]

[illegible]

$$[illegible]$$

[illegible]

$$[illegible]$$

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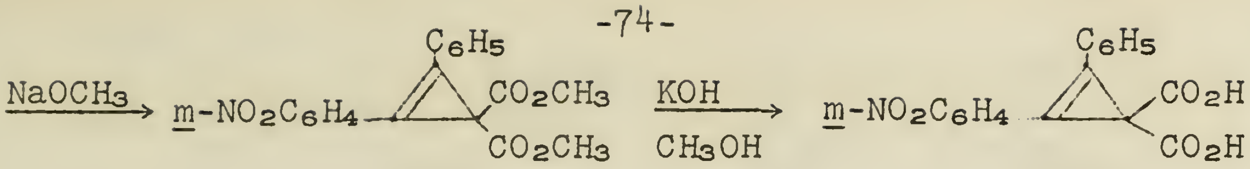


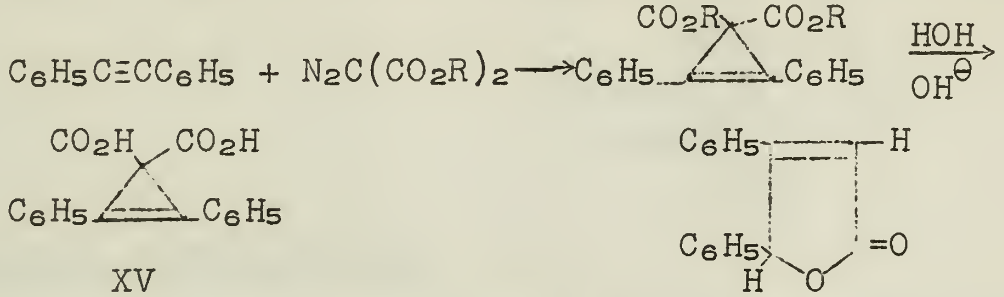
XII XIII

acid XIII. Oxidation of XIII with alkaline potassium permanganate gave nitrodibenzoylmethane (XIV). Darling and Spanagel (26)

$$\text{XIII} \xrightarrow[\text{KMnO}_4]{\text{alk.}} \underline{\text{m}}\text{-NO}_2\text{C}_6\text{H}_4\text{COCH}_2\text{COC}_6\text{H}_5$$

XIV

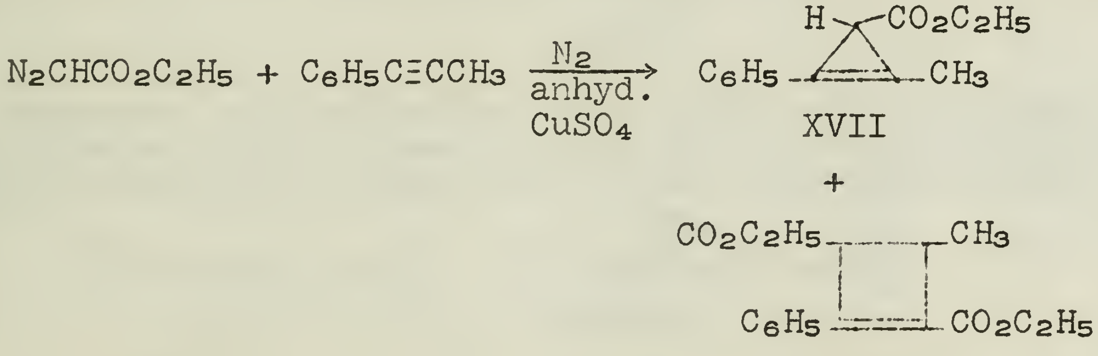
prepared dimethyl 1,2-diphenylcyclopropenedicarboxylate by elimination of nitrous acid from the corresponding nitrocyclopropane. Breslow and Winter (27) have also prepared 1,2-diphenylcyclopropenedicarboxylic acid (XV) by the reaction of diazomalonic ester with diphenyl-



XV XVI

acetylene followed by alkaline hydrolysis. The acid upon melting decarboxylates to a neutral lactone with structure XVI.

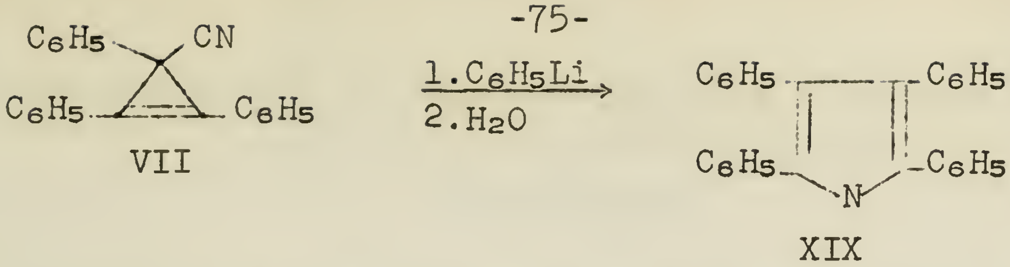
D'yakonov and Komendantov (28) reported the synthesis of ethyl 2-methyl-3-phenyl-cyclopropenecarboxylate (XVII) in 41% yield from phenylmethylacetylene and ethyl diazoacetate. Hydrogenation of the cyclopropene ester gave a mixture of stereoisomeric ethyl 2-methyl-3-phenyl-1-cyclopropanecarboxylates. The saturated ester was also prepared from ethyl diazoacetate and 1-phenylpropene. Diethyl 2-phenyl-4-methyl-1-cyclobutene-1,3-dicarboxylate (XVIII) was also reported as one of the products obtained from the reaction of phenylmethylacetylene and ethyl diazoacetate. This product may have been



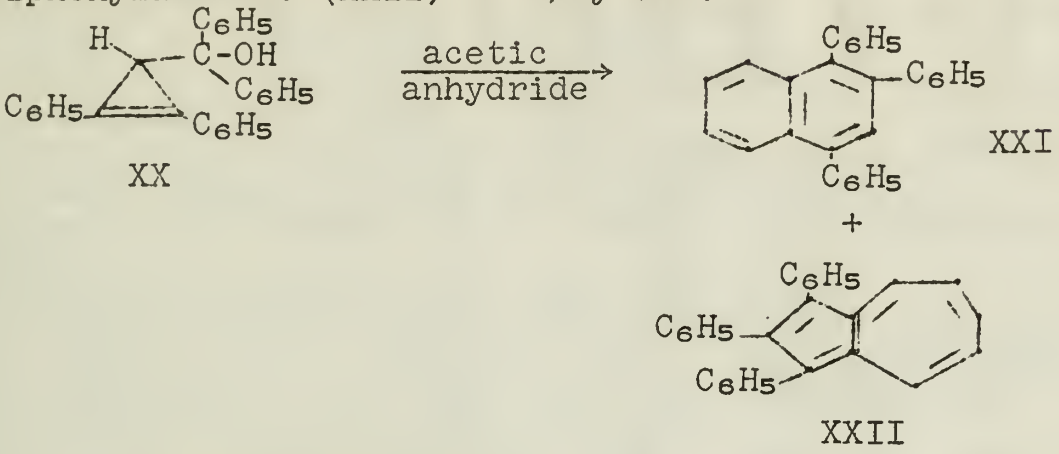
XVII XVIII

formed by the reaction of XVII with diazoacetic ester. Further investigation will be necessary, however, to determine the origin of the cyclobutene derivative.

Reaction of 1,2,3-triphenylcyclopropenyl cyanide (VII) with phenyl lithium and subsequent neutral hydrolysis yields tetraphenyl pyrrole (XIX)(23). Dehydration of carbinol XX (29) with acetic



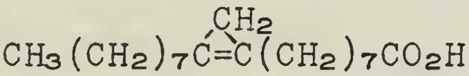
anhydride yields 1,2,4-triphenylnaphthalene (XXI) in 80% yield and 1,2,3-triphenylazulene (XXII) in 6% yield.



A NATURAL PRODUCT: STERCULIC ACID

The natural product, sterculic acid (XXIII), may be isolated from the seeds of Sterculia foetida (30), Sterculia urens (31) and Sterculia apetala (31). Ozonolysis of this acid gives 9,11-diketononadecanoic acid (32), which has been synthesized (33). Hydrogenation gives cis-9,10-methyleneoctadecanoic acid (dihydrosterculic acid)(30) which has also been synthesized (34).

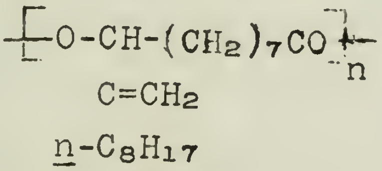
The infrared spectrum of sterculic acid shows absorption at 1010 cm.$^{-1}$, but none at 1645 cm.$^{-1}$(30). The nuclear magnetic resonance spectrum indicates that no vinyl hydrogen is present (35). The chemical and spectral evidence indicate that the correct structure of sterculic acid is that of 2-n-octyl-1-cyclopropeneoctanoic acid (XXIII).



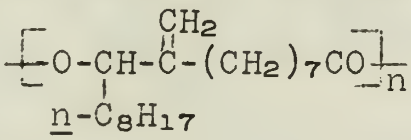
$$CH_3(CH_2)_7\overset{CH_2}{C{=}C}(CH_2)_7CO_2H$$

XXIII

Sterculic acid polymerizes slowly at room temperature to give the polymeric sterculic acid esters of 9-hydroxy-10-methylene and 10-hydroxy-9-methylene-octadecanoic acids (XXIV and XXV)(36).



$$\left[-O-\underset{\underset{n\text{-}C_8H_{17}}{C=CH_2}}{CH}-(CH_2)_7CO- \right]_n$$



$$\left[-O-\underset{n\text{-}C_8H_{17}}{CH}-\overset{CH_2}{\overset{\|}{C}}-(CH_2)_7CO- \right]_n$$

XXIV XXV

Acetic acid reacts with sterculic acid to give the acetic acid esters of 9-hydroxy-10-methylene-and 10-hydroxy-9-methylene-octadecanoic acids (XXVI and XXVII). Ozonolysis of the mixture of XXVI and XXVII yields 9-acetoxy-10-keto-and 10-acetoxy-9-keto-octadecanoic acids (XXVIII and XXIX), which upon treatment with base yield 9-hydroxy-10-keto-and 10-hydroxy-9-keto-octadecanoic acids (XXX and XXXI). Oxidation of both XXX and XXXI with chromic acid yields

9,10-diketooctadecanoic acid, which has been synthesized from oleic acid.

****

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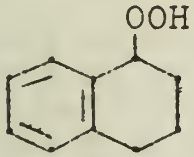
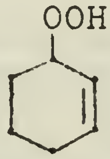
THE PREPARATION AND DECOMPOSITION OF HYDROPEROXIDES

Reported by T. Van Auken April 9, 1959

Hydroperoxides have been commonly prepared by three different methods. Benzyl and allyl type hydroperoxides have been prepared by the oxidation of the corresponding hydrocarbons with oxygen. Tetralin hydroperoxide (I) and cyclohex-2-ene-1-hydroperoxide (II) are prepared this way (1,2). Certain saturated hydrocarbons are also oxidized to hydroperoxides in this manner. Isobutane is oxidized to t-butyl hydroperoxide by oxygen with hydrogen bromide as a catalyst (3). Hydroperoxides may also be prepared by the alkylation of hydrogen peroxide with a carbonium ion. This is usually done by treating a suitable alcohol with 30 or 90% hydrogen peroxide and concentrated sulfuric acid. 1,3,3-Trimethylcyclohexyl hydrogen peroxide (III) has been prepared this way (4). The third method is the displacement of a suitable leaving group with the perhydroxyl anion. For example, ethyl hydroperoxide has been prepared by the treatment of diethyl sulfate with hydrogen peroxide in alkaline solution (5).


I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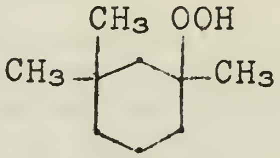
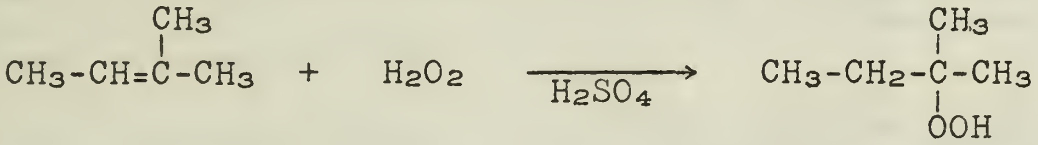

III

$$C_2H_5\text{-}O\text{-}SO_2\text{-}O\text{-}C_2H_5 + H_2O_2 \xrightarrow[OH^-]{} C_2H_5\text{-}OOH + C_2H_5\text{-}SO_3H$$

These older methods for the preparation of hydroperoxides have been reviewed elsewhere (8-12), and consequently only more recent developments and extensions of the older work will be discussed here.

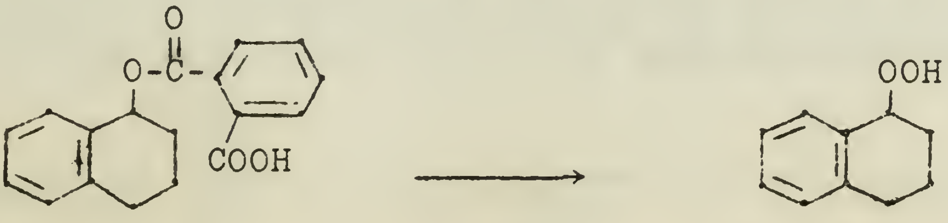
EXTENSION OF THE PREPARATION OF HYDROPEROXIDES THROUGH CARBONIUM IONS

Compounds other than alcohols can be used to generate carbonium ions for the alkylation of hydrogen peroxide. Davies and his coworkers have extended Milas' work with alcohols to olefins, esters, and ethers. Treatment of 2-methylbutene-2 with 90% hydrogen peroxide and sulfuric acid produces 2-methyl-2-butyl hydroperoxide (IV) (6), while 1,2,3,4-tetrahydronaphthyl hydrogen phthalate is converted to tetralin hydroperoxide in 81% yield by 90% hydrogen peroxide and a small amount of sodium bicarbonate (6). Some ethers will also form

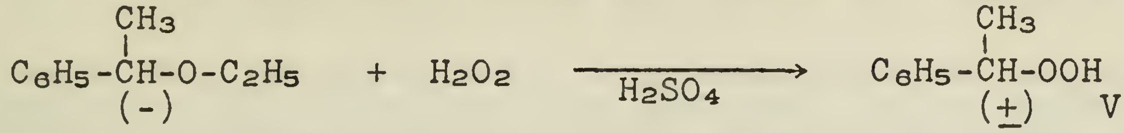


$$CH_3\text{-}CH\text{=}\overset{CH_3}{\overset{|}{C}}\text{-}CH_3 + H_2O_2 \xrightarrow[H_2SO_4]{} CH_3\text{-}CH_2\text{-}\underset{OOH}{\underset{|}{\overset{CH_3}{\overset{|}{C}}}}\text{-}CH_3$$

IV


I

hydroperoxides on treatment with 90% hydrogen peroxide and sulfuric acid. Ethyl α-phenylethyl ether is converted by this treatment into



$$\underset{(-)}{C_6H_5\text{-}\overset{\overset{\displaystyle CH_3}{|}}{C}H\text{-}O\text{-}C_2H_5} + H_2O_2 \xrightarrow[H_2SO_4]{} \underset{(\pm)}{C_6H_5\text{-}\overset{\overset{\displaystyle CH_3}{|}}{C}H\text{-}OOH} \quad V$$

α-phenylethyl hydroperoxide (V)(7). Racemization has been established in this case with the levorotatory ether.

THE PREPARATION OF HYDROPEROXIDES BY NUCLEOPHILIC DISPLACEMENT

Until recently primary hydroperoxides have been essentially unavailable. The first two methods mentioned in the introduction are limited to secondary and tertiary hydroperoxides, and the last method is limited to the lower members of the series by solubility problems. Linstrom has extended the method to n-butyl and s-butyl hydroperoxides by the use of aqueous methanol as a solvent (13).

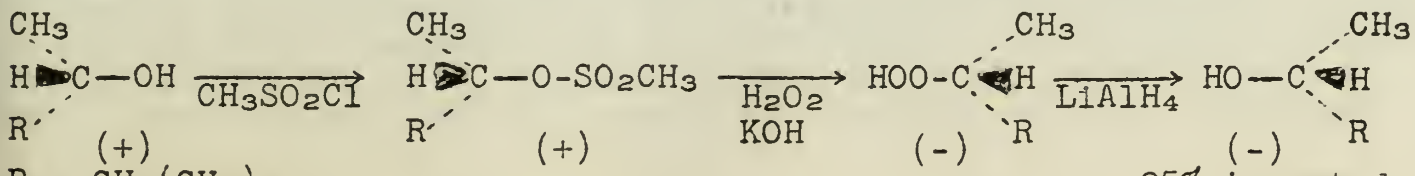
Williams and Mosher have developed a practical method for the preparation of primary hydroperoxides which is not restricted to the lower members of the series (14). When n-alkyl methanesulfonates (VI) are treated with 30% hydrogen peroxide in an alkaline solution of aqueous methanol, the corresponding hydroperoxides are formed. The n-alkyl methanesulfonates are readily prepared by treatment of the corresponding alcohols with methanesulfonyl chloride and pyridine (15). The series of normal alcohols from n-propyl through n-decyl have been converted to the corresponding hydroperoxides in over-all yields ranging from 26 to 46%.

$$ROH + CH_3SO_2Cl + C_5H_5N \longrightarrow \underset{VI}{CH_3SO_2\text{-}OR} + C_5H_5N\cdot HCl$$

$$CH_3SO_2\text{-}OR + H_2O_2 \xrightarrow[\substack{KOH \\ CH_3OH\text{-}H_2O}]{} CH_3SO_3H + ROOH$$

Secondary alcohols can also be converted to the corresponding hydroperoxides by this method although the yields are lower than those obtained with primary alcohols (16). The best yields of secondary hydroperoxides were obtained when one of the groups attached to the carbinol carbon was methyl. Larger groups gave lower yields. For example 2-hexyl alcohol was converted to 2-hexyl hydroperoxide in 20% over-all yield, with the last step going in 25% yield, but 3-hexyl alcohol gave a 7% over-all yield of 3-hexyl hydroperoxide since the last step proceeded in only 9% yield.

The decreased yields obtained from the more hindered methanesulfonates are indicative of an S_N2 mechanism. Such a mechanism was established by the following evidence. Crude rate studies established the order of rates of hydroperolysis as n-butyl > s-butyl > isobutyl and n-heptyl > 2-heptyl > 4-heptyl (16). Inversion of configuration during the formation of the hydroperoxide was established by the conversion of (+)-2-heptanol to (-)-2-heptanol which was 95% inverted by the reaction sequence shown below (17). The carbon-oxygen bond is not



R = $CH_3(CH_2)_4$-

95% inverted

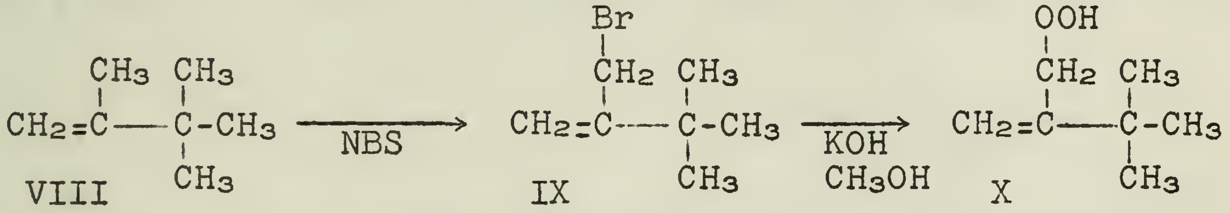
broken during the formation of the methanesulfonate, and Davies has shown that the final reduction takes place with retention (18,19) as expected, so inversion must occur during the hydroperoxide formation.

One of the more interesting compounds which has been prepared by this method is allyl hydroperoxide (VII)(20). Allyl methanesulfonate could not be prepared satisfactorily by the usual method, but it was obtained by treatment of an ether solution of sodium alloxide and allyl alcohol with methanesulfonyl chloride. Allyl hydroperoxide was then obtained in 30-40% yield. Because of the ready decomposition of this compound, it was purified by vapor phase chromatography. Even ordinary incandescent illumination will cause allyl hydroperoxide to decompose. On distillation it leaves a highly explosive, polymeric residue.

$$CH_2{=}CH\text{-}CH_2\text{-}OOH$$

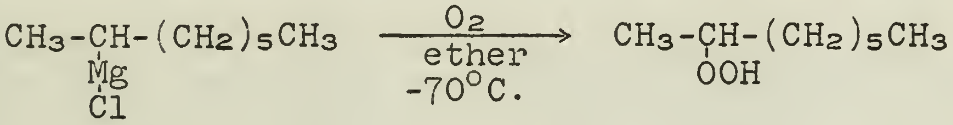
VII

Hydroperoxides can be prepared by displacing other leaving groups with the perhydroxyl anion. Hoffman has prepared 2-t-butylallyl hydroperoxide (X) in 65% yield by treating the corresponding bromide (IX) with 30% hydrogen peroxide in an aqueous methanolic solution of potassium hydroxide (21). The bromide was prepared from 2,3,3-trimethylbutene-1 (VIII) by treatment with N-bromosuccinimide.



THE PREPARATION OF HYDROPEROXIDES VIA THE GRIGNARD REAGENT

Walling has developed an excellent method for the preparation of hydroperoxides from the corresponding Grignard compounds (22,23). In this method the Grignard reagent is oxidized to the corresponding hydroperoxide by slowly adding an ethereal solution of the reagent to an equal volume of oxygen-saturated ether at -70°. The yield is very sensitive to the reaction conditions. An excess of the Grignard at any time must be avoided since it reduces the salt of the hydroperoxide which has just been formed. For this reason inverse addition (addition of the Grignard *to* the oxygen solution) is used, and the addition is made slowly. An increase in the temperature also reduces the yield. Although the best yields are obtained with tertiary and secondary compounds, the method is also applicable to primary compounds. Ethyl and benzyl hydroperoxides have been prepared by this method in yields of 57% and 30%. The method is not restricted to the Grignard reagent. *n*-Butyllithium and di-*n*-butylzinc have also been used to prepare *n*-butyl hydroperoxide, but the yields are inferior to those obtained



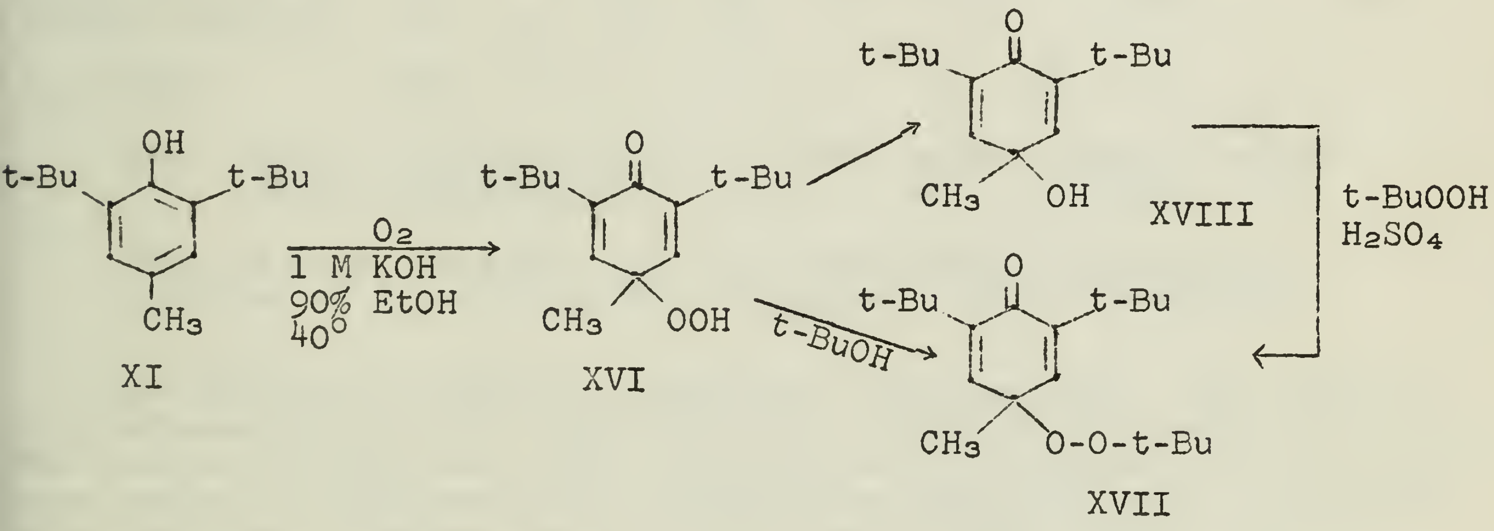
$$CH_3\text{-}\underset{\underset{Cl}{Mg}}{CH}\text{-}(CH_2)_5CH_3 \xrightarrow[\text{-70°C.}]{O_2\ \text{ether}} CH_3\text{-}\underset{OOH}{CH}\text{-}(CH_2)_5CH_3$$

$$R\text{-}OO\text{-}Mg\text{-}X \quad + \quad R\text{-}Mg\text{-}X \longrightarrow 2\ R\text{-}O\text{-}Mg\text{-}X$$

with the Grignard compound. When aryl Grignards were used, no aryl hydroperoxides were isolated, but titration indicated peroxides in yields of up to 9%. From phenylmagnesium bromide, phenol (41%), α-phenylethanol (7%), and biphenyl (11%) were also obtained. These products can be explained on the basis of radical decomposition of aryl hydroperoxides.

When the oxidation of the Grignard reagent is carried out in the presence of a small amount of acetone, the yield of hydroperoxide is not reduced significantly, and even when acetone is used for the solvent for oxygen, a 60% yield can be obtained. Thus the reaction between the Grignard compound and oxygen must be extremely rapid. The addition of *n*-butyraldehyde or diphenylamine to the reaction mixture does not decrease the yields, and no *n*-butyric acid is formed. Similarly, when phenylmagnesium bromide is oxidized in the presence of cumene, no peroxides are formed. These experiments indicate that the oxidation of the Grignard reagent by air is probably not a free radical reaction, but such a mechanism is not definitely ruled out.

An interesting parallel to the preparation of hydroperoxides from the Grignard reagent is the conversion of 2,6-di-*t*-butyl-4-methylphenol (XI) to the hydroperoxide XVI by the action of oxygen in one molar ethanolic potassium hydroxide (23a). The structure of XVI was



established by conversion to the corresponding alcohol XVIII, and to the peroxide XVII, which was synthesized by another route (23b). In view of the reaction conditions, it seems probable that the mechanism involves the addition of oxygen to a carbanion.

THE DECOMPOSITION OF *n*-BUTYL HYDROPEROXIDE

Wurster, Durham, and Mosher have studied the thermal decomposition of *n*-butyl hydroperoxide, a complex system which produces a multitude of products (24). The principal products, *n*-butyric acid, hydrogen, *n*-butyl *n*-butyrate, and water account for about 80% of the hydroperoxide decomposed. Smaller amounts of *n*-butyraldehyde, *n*-butyl alcohol, and a number of fragmentation products were also found. Similar results were also obtained with isobutyl hydroperoxide. The products of these decompositions are tabulated in the table.

Products of the Decomposition of *n*-Butyl Hydroperoxide

	n-BuOOH	iso-BuOOH	*n*-BuOOH	*n*-BuOOH + 4.5% TsOH	*n*-BuOOH + U.V. light	*n*-BuOOH + .756 mol. PrCHO	*n*-BuOOH + AmCHO	BuOO$\overset{OH}{\overset{\mid}{C}}$HPr	same cpd. + 10% TsOH	same cpd. + U.V. light
Temperature, °C.	86°	86°	100°	100°	25-36°	86°	86°	86°	86°	35°
Hydrogen	.45	.63	.41	.18	.015	.37	.50	.52	.11	.02
Propane	.03	.06	.05	.12	.14	.13	.05	.13	.10	.29
Carbon Dioxide	.022	.038	.044	.051	.020	.012	.018	.12	.02	.049
Carbon Monoxide	.017	.040	.004	.021	.015	.038	.046	.020	.02	.085
Oxygen	.006	.003	.012	.009	.003	.007	.002	---	--	.004
Butyric Acid	.50	.62	.4	.03	.13	.62		.76	.02	.26
Water	.44	.23	.5	1.4	--	.02		.06	.68	--
Butyl Butyrate	.15	.05	.14	.24	.05	.18		.24	.42	.12
Butyraldehyde	.01	.06	.02	.02	--	.33		.27	.12	.12
Butyl Alcohol	.04	.06	.1	.09	.39	.31		.23	.23	.43
Butyl Formate	.01	.03	.01	.06	.18	.04		.05	.23	.45
Propionic Acid	.01	--	.02	.02	--	--				
Butyl Propionate	.tr	--	.01	.02	.013	.01		.02		.02
Propyl Butyrate	.tr	--	.01	.01						
$t_{1/2}$, hours	24	8	5	3		4	6	4		

Key: TsOH = *p*-toluenesulfonic acid AmCHO = caproaldehyde
PrCHO = butyraldehyde tr = trace

Results given in moles/mole of hydroperoxide decomposed.
Analyses of liquids by VPC; of gases by Orsat techniques.

The effects of different catalysts were examined. The addition of *p*-toluenesulfonic acid appears to have catalyzed the ester-producing reaction at the expense of the hydrogen and acid producing reactions, since under its influence the products are very different. Similarly, base completely changes the course of the decomposition. With 1% potassium hydroxide the only reported product is *n*-butyl alcohol. Apparently in the non-catalyzed decomposition there are two principal reactions. Hydrogen and butyric acid are produced by a reaction which is not catalyzed by acid, while *n*-butyl *n*-butyrate is produced by a competing, acid-catalyzed reaction.

In order to study the hydrogen-producing reaction further, *n*-butyl deuteroperoxide was decomposed. No deuterium or hydrogen deuteride was found in the hydrogen evolved, showing that the hydroperoxide hydrogen is not involved in the formation of hydrogen. In further studies a plot of $1-V/V_{final}$ vs. time, where V is the volume of gas evolved, was made for each decomposition. From this the half life of the hydrogen producing reaction, $t_{1/2}$, was determined. These measurements also revealed that the reaction has an induction period which may be eliminated by the addition of aldehydes, but not ketones. When *n*-butyraldehyde was added, less than half of it appeared in the products, and when *n*-caproaldehyde was added, n-caproic acid and *n*-butyraldehyde appeared in the products. This suggests that aldehyde is being formed during the induction period, and once formed, it

reacts with the hydroperoxide to form an intermediate which decomposes to products and more aldehyde. Furthermore, the aldehyde entering into the intermediate reappears as acid rather than aldehyde, while the hydroperoxide is converted to aldehyde.

As a possible intermediate, Durham, Wurster, and Mosher considered *n*-butyl 1-hydroxybutyl peroxide (XIX), which they found was readily formed by the addition of *n*-butyl hydroperoxide to n-butyraldehyde at room temperature without a catalyst (25). A similar addition to acetone was found to require an acid catalyst. On thermal

$$\mathrm{RCHO} + \mathrm{RCH_2OOH} \longrightarrow \overset{\mathrm{OH}}{\mathrm{RCH}}\text{-}\mathrm{OO}\text{-}\mathrm{CH_2R}$$

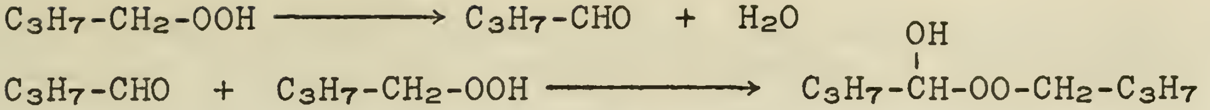
XIX

decomposition this compound was found to give products qualitatively the same as those from *n*-butyl hydroperoxide alone, and almost identical to those given by a mixture of *n*-butyl hydroperoxide and *n*-butyraldehyde. *n*-Butyl 1-hydroxybutyl peroxide decomposes without an induction period, and with a half life identical to that of the hydroperoxide-aldehyde mixture. It should be pointed out, however, that the identical behavior of the proposed intermediate and the hydroperoxide-aldehyde mixture does not support the intermediacy of this compound, since in view of its ready formation from the aldehyde and the hydroperoxide, a mixture of the two would be expected to be identical with the compound itself. Although *n*-butyl 1-hydroxybutyl peroxide has been shown to decompose to approximately the same products as the hydroperoxide, it has not been isolated from the reaction mixture, so its intermediacy pivots on the assumption that *n*-butyraldehyde is formed during the induction period. This assumption is supported by the isolation of small quantities of the aldehyde among the products and by the isolation of aldehydes in good yield from the thermal decomposition of other primary hydroperoxides (21,26).

While it would not be expected that hydrogen would be formed through atomic hydrogen, Durham, Wurster, and Mosher have carefully established that no atomic hydrogen is formed during the decomposition. When the reaction was carried out in the presence of methylene blue, an indicator for atomic hydrogen (27,28), the indicator was not decolorized, while control reactions known to form atomic hydrogen decolorized the indicator in a matter of seconds. Furthermore, when the decomposition was carried out under a deuterium atmosphere, no hydrogen deuteride was formed. If atomic hydrogen were formed, hydrogen deuteride would be expected from the low energy of activation of the exchange reaction (29).

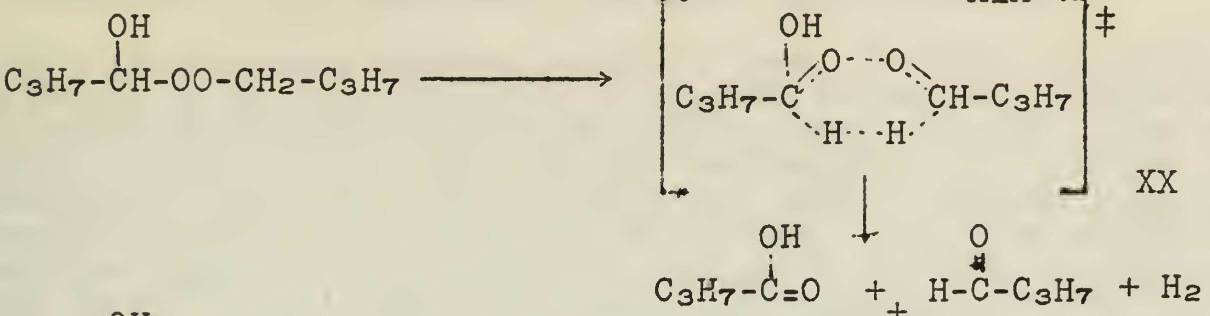
Mosher and his co-workers have proposed the following mechanism for the thermal decomposition of *n*-butyl hydroperoxide. During the induction period *n*-butyl hydroperoxide dehydrates to *n*-butyraldehyde. The hydroperoxide immediately adds to the aldehyde to form 1-butyl 1-hydroxybutyl peroxide (XIX). Because the hydroperoxide is present in large excess, only a small, steady-state concentration of the aldehyde ever builds up. The intermediate XIX can decompose by two different routes. In the absence of acid it decomposes through the cyclic transition state XX to *n*-butyric acid, *n*-butyraldehyde, and hydrogen. The aldehyde formed this way then continues the chain reaction. In the presence of acid, decomposition can also take place by the competitive route F to form *n*-butyl *n*-butyrate and water. Mosher and his co-workers have suggested that ester must be formed

$$C_3H_7\text{-}CH_2\text{-}OOH \longrightarrow C_3H_7\text{-}CHO + H_2O$$ C)



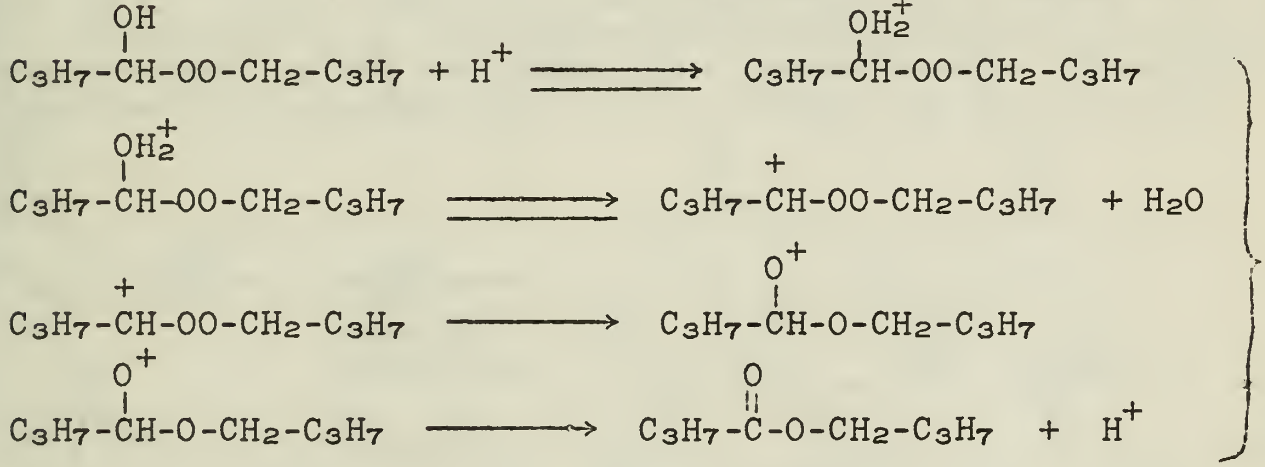
$$C_3H_7\text{-}CHO + C_3H_7\text{-}CH_2\text{-}OOH \longrightarrow C_3H_7\text{-}\overset{OH}{\overset{|}{C}}H\text{-}OO\text{-}CH_2\text{-}C_3H_7$$ D)

XIX



$$C_3H_7\text{-}\overset{OH}{\overset{|}{C}}H\text{-}OO\text{-}CH_2\text{-}C_3H_7 \longrightarrow C_3H_7\text{-}\overset{OH}{\overset{|}{C}}{=}O + H\text{-}\overset{O}{\overset{\|}{C}}\text{-}C_3H_7 + H_2$$ E)

XX



$$C_3H_7\text{-}\overset{OH}{\overset{|}{C}}H\text{-}OO\text{-}CH_2\text{-}C_3H_7 + H^+ \rightleftharpoons C_3H_7\text{-}\overset{OH_2^+}{\overset{|}{C}}H\text{-}OO\text{-}CH_2\text{-}C_3H_7$$

$$C_3H_7\text{-}\overset{OH_2^+}{\overset{|}{C}}H\text{-}OO\text{-}CH_2\text{-}C_3H_7 \rightleftharpoons C_3H_7\text{-}\overset{+}{C}H\text{-}OO\text{-}CH_2\text{-}C_3H_7 + H_2O$$

$$C_3H_7\text{-}\overset{+}{C}H\text{-}OO\text{-}CH_2\text{-}C_3H_7 \longrightarrow C_3H_7\text{-}\overset{O^+}{\overset{|}{C}}H\text{-}O\text{-}CH_2\text{-}C_3H_7$$

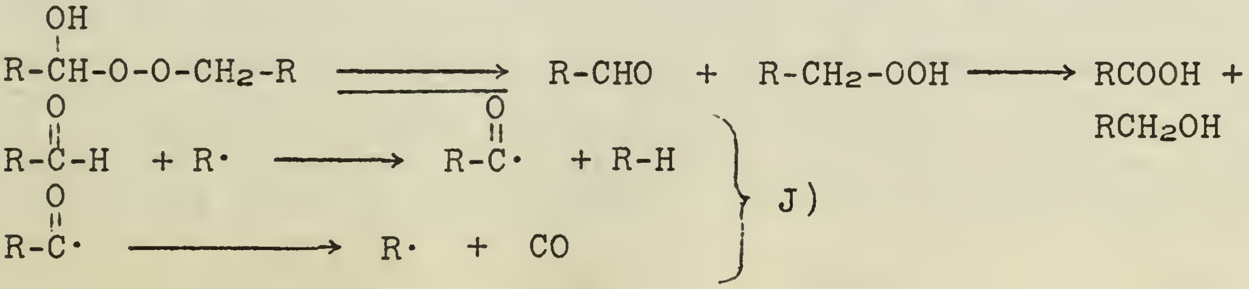
$$C_3H_7\text{-}\overset{O^+}{\overset{|}{C}}H\text{-}O\text{-}CH_2\text{-}C_3H_7 \longrightarrow C_3H_7\text{-}\overset{O}{\overset{\|}{C}}\text{-}O\text{-}CH_2\text{-}C_3H_7 + H^+$$ F)

by a mechanism other than ordinary esterification since the formation of acid which is to undergo esterification requires the evolution of an equivalent amount of hydrogen according to route E. This is not observed in the acid catalyzed decompositions, where apparently route F is the predominant mode of decomposition. Of course, *n*-butyric acid might be formed by a route other than E. In support of their proposed mechanism Durham and Mosher have recently offered kinetic studies (30). They have reported the evolution of hydrogen from isobutyl 1-hydroxyisobutyl peroxide in α-methylstyrene to be first order in peroxide for 60% or more of the decomposition.

There are certain experimental facts which differ from those predicted by this mechanism. One such case is the failure of *n*-butyl 1-hydroxybutyl peroxide to give equimolar amounts of hydrogen, butyric acid, and butyraldehyde as predicted by equation E. Durham, Wurster and Mosher have suggested that this can be explained by the disproportionation of butyraldehyde to butyl alcohol and butyric acid according to equation G, or by a free radical oxidation of aldehyde

$$2\ RCHO \longrightarrow RCOOH + R\text{-}CH_2\text{-}OH$$ G)

by the hydroperoxide. The latter suggestion is probably the better since a reaction such as H could account for the high yield of acid and the formation of alcohol, while free radical decarbonylation of the aldehyde, as in J, could account for the low yield of aldehyde. It should be noted that H does not need to involve reversal of the



$$R\text{-}\overset{OH}{\overset{|}{C}}H\text{-}O\text{-}O\text{-}CH_2\text{-}R \rightleftharpoons R\text{-}CHO + R\text{-}CH_2\text{-}OOH \longrightarrow RCOOH + RCH_2OH$$ H)

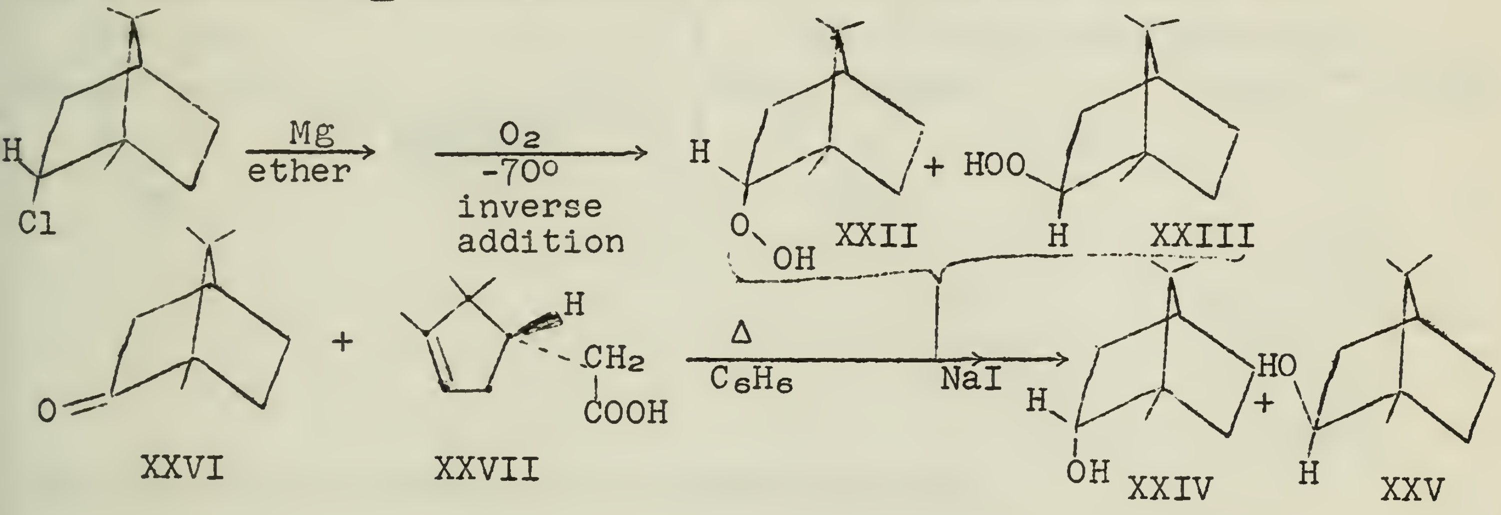
$$R\text{-}\overset{O}{\overset{\|}{C}}\text{-}H + R\cdot \longrightarrow R\text{-}\overset{O}{\overset{\|}{C}}\cdot + R\text{-}H$$

$$R\text{-}\overset{O}{\overset{\|}{C}}\cdot \longrightarrow R\cdot + CO$$ J)

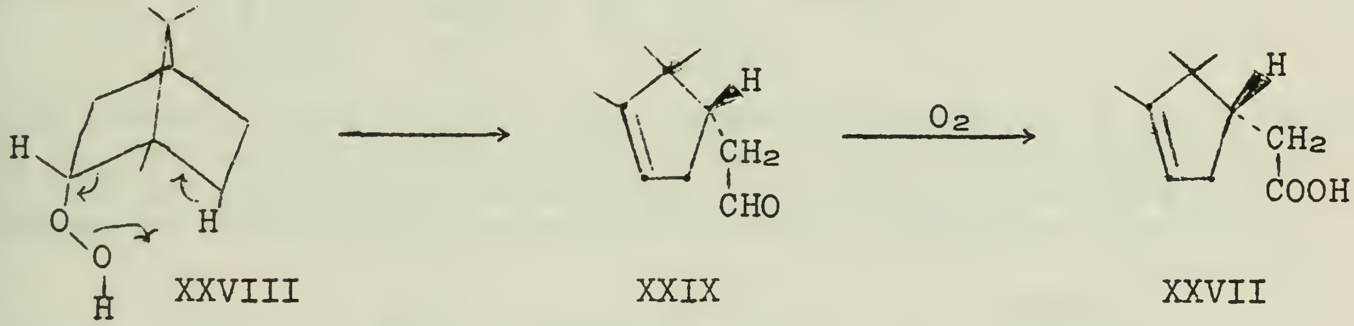
formation of the hydroxy peroxide since the same products can be explained on the basis of the homolytic cleavage of the peroxide bond.

THE DECOMPOSITION OF BORNYL AND ISOBORNYL HYDROPEROXIDES

When the Grignard reagent prepared from *ℓ*-bornyl chloride (XXI) was oxidized by Walling's method, a mixture of bornyl hydroperoxide (XXII) and isobornyl hydroperoxide (XXIII) resulted (32). On treatment with sodium iodide, this mixture was reduced to a mixture of 56% *ℓ*-borneol (XXIV) and 44% *d*-isoborneol (XXV), thereby establishing the composition of the hydroperoxide mixture. When the hydroperoxide mixture was thermally decomposed in refluxing benzene, it gave *ℓ*-camphor (XXVI) in 60% yield and *ℓ*-α-campholenic acid (XXVII) in 33% yield. Decomposition of the same hydroperoxide mixture in base gave the same products in 48% and 34% yields, respectively. To explain the formation of *ℓ*-α-campholenic acid, Walling and Buckler have



suggested the concerted mechanism described by XXVIII, leading to *ℓ*-α-campholenaldehyde (XXIX). This aldehyde would then undergo autoxidation to the corresponding acid. A consequence of this mechanism is that *ℓ*-α-campholenic acid should be formed by the endo hydroperoxide (XXII) only. The separation of the hydroperoxide was not achieved, so this point could not be verified.



SOLVOLYTIC DECOMPOSITION OF ARYLSULFONATES OF HYDROPEROXIDES

Bartlett and Storey have recently shown that *t*-butyl arylpersulfonates (XXX) decompose almost quantatively to acetone and the corresponding arylsulfonic acid in methanol (32). The reaction has been shown to proceed *via* the ionic fission of the oxygen-oxygen bond by the following evidence. A plot of the Hammett equation for this reaction gives a ρ of +1.36. The corresponding value for the 9-decalyl perbenzoates, which are known to rearrange through an ionic mechanism (33), is +1.36. The rate of the reaction increases with the solvolyzing power of the solvent. A plot of the Grunwald-Winstein

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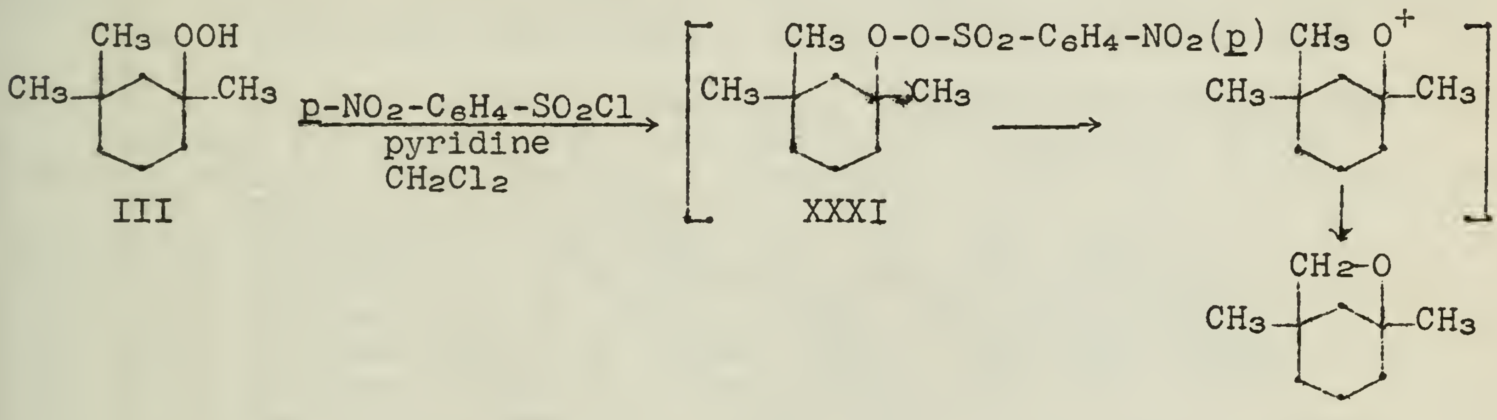
equation gives a value of m of +0.44. The 9-decalyl perbenzoates give a value of m of +0.57. When the reaction is run in styrene, the solvent is not polymerized.

$$t\text{-Bu-O-O-}SO_2Ar \longrightarrow t\text{-Bu-}O^+ + {}^-O\text{-}SO_2Ar \longrightarrow CH_3COCH_3 + ArSO_3H$$

Using this method to generate a positively charged oxygen, Corey and White have demonstrated a unique case of electrophilic attack on a saturated carbon atom. Treatment of 1,3,3-trimethylcyclohexyl hydroperoxide (III) with p-nitrobenzenesulfonyl chloride and pyridine in methylene chloride gives the bicyclic ether XXXII. Intermediate in this reaction is the p-nitrobenzene sulfonate XXXI, which decomposes to give a cationic oxygen. The bicyclic ether XXXII has been synthesized unequivocally.



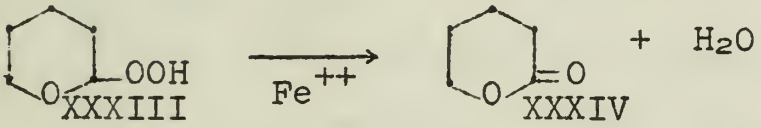
III

XXXI

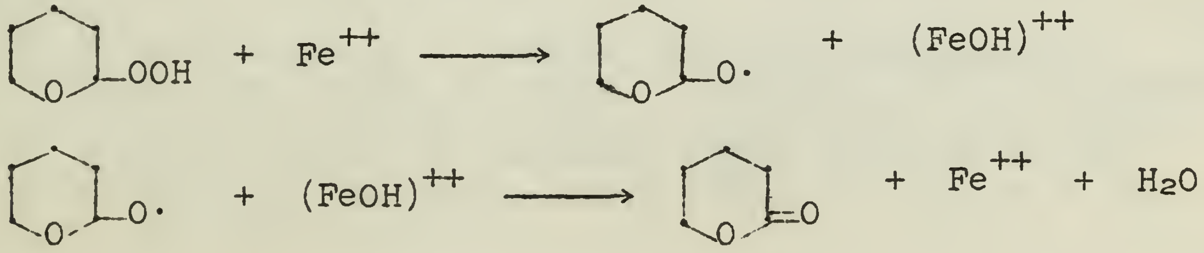
XXXII

THE CATALYTIC DECOMPOSITION OF HYDROPEROXIDES

In the presence of certain transition metals hydroperoxides are decomposed to alkoxide radicals, which undergo further reaction to the observed products. For example, 2-hydroperoxytetrahydropyran (XXXIII) has been converted to δ-valeroactone (XXXIV) by treatment with ferrous sulfate (34). The suggested mechanism is shown below. It is also possible that the last step occurs by disproportionation of XXXV to hemiacetal and lactone, since ferric hydroxide and 2-hydroxytetrahydropyran were also reported among the products.



XXXIII XXXIV



XXXV

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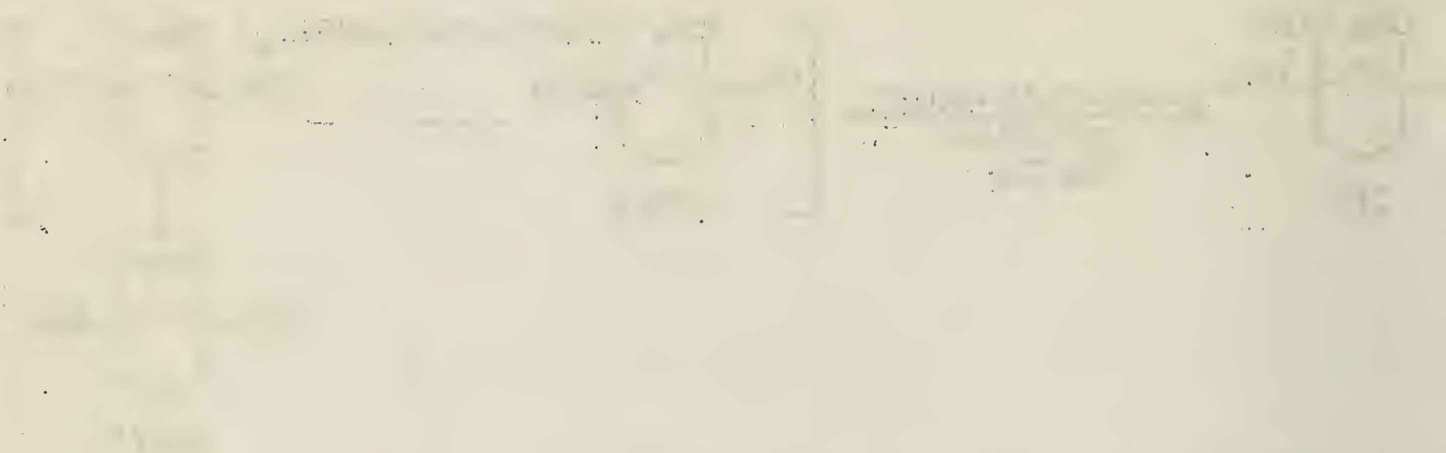

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HOMOLYTIC AROMATIC SUBSTITUTION: ISOTOPE EFFECTS AND MECHANISM

Reported by R. E. Pearson April 13, 1959

In reactions where substitution takes place on an aromatic nucleus by means of free radicals (e.g. $\mathrm{Ar\cdot + Ar'H \longrightarrow ArAr'}$ + other products), the kinetic isotope effect (1) has been utilized to gain information concerning the mechanism. The determination of this effect, however, is not a simple matter and few of the reported results have been unequivocal. This seminar will review some of the evidence obtained in support of a generally accepted mechanism, including orientation and product studies and the additional information gained by examination of the isotope effects.

The most common method for causing radical substitution of an aromatic nucleus has been the decomposition of alkyl or aroyl peroxides in an aromatic solvent. In many cases, a substantial amount of tar and polyphenyls have been formed. The products of interest, however, have been the biphenyls produced, usually in less than 40% yield. When substitution has been introduced into the substrate, only monosubstituted biphenyls have been found (2).

Following the initial step, which is undoubtedly the decomposition of the peroxide into aryl or aroyloxy fragments, designated here as Ar·, the following steps might take place:

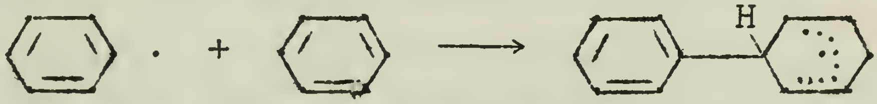
$$\text{(A)}\quad \mathrm{Ar\cdot + Ar'H \longrightarrow ArAr' + H\cdot \xrightarrow{Ar\cdot} ArH}$$

$$\text{or (B)}\quad \mathrm{Ar\cdot + Ar'H \longrightarrow ArH + Ar'\cdot \xrightarrow{Ar\cdot} ArAr'}$$

$$\text{or (C)}\quad \mathrm{Ar\cdot + Ar'H \longrightarrow Ar\dot{A}r'H \xrightarrow{Ar\cdot} ArAr' + ArH}$$

In (A), the reaction producing a hydrogen atom would be strongly endothermic, and thus unlikely. Attempts to find evidence for the existence of free hydrogen atoms by their action on reducible compounds in solution have usually proved futile. The failure to detect disubstituted biphenyls, at least with simple substrates, is evidence against the second scheme. If hydrogen abstraction is important, solvent radicals would be formed, leading to dimeric product.

The third scheme is the one generally accepted, and it will be seen that most of the evidence gained from studying the reaction is in support of this mechanism. The energetics of this reaction, forming an activated radical complex, are unknown, but the loss of resonance energy upon addition of the radical to the aromatic nucleus



may be made up by the formation of a new carbon-carbon bond and by delocalization of a π-electron in the resulting allylic radical.

SIMPLE AROMATIC SYSTEMS

A series of experiments by Hey, Williams, and co-workers (3) has provided the relative reactivities of a number of substituted benzenes toward various attacking radicals derived from substituted benzoyl peroxides, and the partial rate factors for reactivities at the three positions on the aromatic ring. These data lead to a comparison of radical and electrophilic aromatic substitution. The following table summarizes their results.

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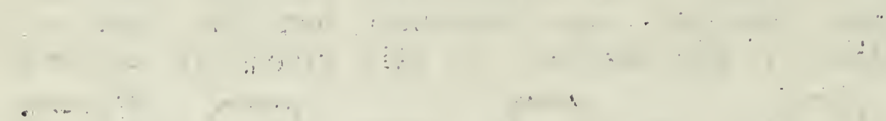

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Table I

Radical	Substrate ($\text{Ø}X$)	$\frac{\text{Ø}X}{\text{Ø}H}K$	Fo	Fm	Fp
p-BrC_6H_4	$\text{Ø}NO_2$	1.8	3.1	0.7	2.9
p-ClC_6H_4	$\text{Ø}NO_2$	1.5	2.7	0.6	2.5
Ø	$\text{Ø}NO_2$	4.0	7.5	1.2	6.6
Ø	ØBr	1.7	2.6	1.7	1.8
p-O_2N-C_6H_4	ØBr	1.5	2.7	1.1	1.3
p-O_2N-C_6H_4	ØCl	1.2	2.1	0.8	1.1
Ø	ØCl	1.4	2.2	1.4	1.6

In the third column are the relative rates of reaction of ØX against those of ØH with the attacking radical. The last three columns are the partial rate factors for the ortho, meta, and para positions of ØX. In practice, the relative rates of reaction were determined against nitrobenzene as reference. For example, a mixture of nitrobenzene and bromobenzene was nitrophenylated, as was a mixture of nitrobenzene and benzene. From these results were obtained the values for the relative rates of reaction of bromobenzene and benzene toward nitrophenylation.

$$\frac{\text{Ø}Br}{\text{Ø}NO_2}K \times \frac{\text{Ø}NO_2}{\text{Ø}H}K = \frac{\text{Ø}Br}{\text{Ø}H}K$$

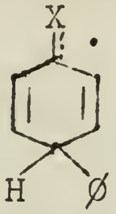
As indicated by these data, the substituents on both the attacking radical and substrate cause polar influences, similar to those found in electrophilic aromatic substitution. In the case of nitrobenzene, all three positions are less reactive toward p-chloro-and p-bromo-phenylation than toward phenylation, the reactivities toward the p-halophenylating agents being about the same. The decrease in reactivity in going from the phenyl to the p-halophenyl radical is more marked in the ortho and para positions than in the meta. In considering these factors, it is seen that they bear similarity to what is known of electrophilic attack on nitrobenzene, where the nitro group withdraws electrons, deactivating the nucleus, with the greatest effect being at the ortho and para positions. The attacking p-halophenyl radicals bear an electron withdrawing group which might be expected to exert a permanent effect on the polarity of the radical, giving it an electrophilic character. Thus a similarity between homolytic and electrophilic substitution can be seen. This discussion depends on the assumption that free radical reactions are subject to polar influences and that the attacking p-halophenyl radicals are electrophilic compared to the "neutral" phenyl radical. The magnitude of the effects indicates the polar effects to be small.

Further confirmation is gained by examination of halobenzenes as solvents. These are less reactive toward substitution by the p-nitrophenyl radical than the non-polarized phenyl radical. Again this is in agreement with the deactivating influences of halogens in electrophilic substitution.

The choice of nitrobenzene as reference solvent helps to validate the competitive method. The objection has been raised that the various processes leading to the formation of resins may cause differential removal of the diaryl products (4). Experimentally the authors found that very little resin was formed, except when only relatively unreactive solvents such as benzene, pyridine, alkyl benzenes, and halobenzenes were employed. Nitro benzene, a "fast" solvent, where used alone or mixed with "slow" solvents, gave very little tar. Thus the criticism is not applicable to this work, where all runs contained

nitrobenzene as one component. As a matter of fact, where pyridine was used in place of nitrobenzene to confirm the results, resins were obtained, but the results still agreed.

To account for the *ortho*, *para*-activation in the phenylation of nitrobenzene, Hey (5) postulates the following resonance contributions to the various transition states:



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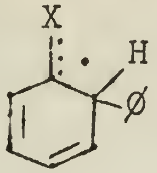

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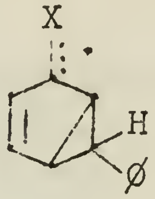
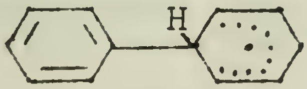


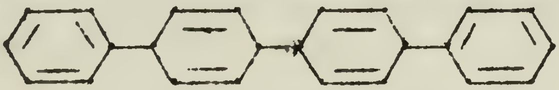
The third structure is of less consequence than the first two, so this is a likely rationale for the greater activation of the positions *ortho* and *para* to a group capable of entering into resonance interaction with the ring, thus stabilizing the unpaired electron. The more favorable *ortho* transition state has been invoked to account for the greater activation of the *ortho* over the *para* position. Another explanation based on the electron density of the substituent has been proposed (6). These structures are activated complexes of the sort suggested above in the general mechanism (c). Observe the similarity to the charged structures (some isolable!) that are intermediates in electrophilic aromatic substitution.

Walling (2) has compiled a table of relative reactivities, isomer distributions, and partial rate factors for reactions of a number of simple aromatic molecules with phenyl radicals derived from benzoyl peroxide. This summary shows that the relative reactivities do not differ by more than a factor of five. The changes which are observed are mainly in the activation of the *ortho* and *para* positions.

Product studies (7) on the phenylation of benzene in dilute solution have led to belief in the existence of the phenylcyclohexadienyl radical (I) as an intermediate in the reaction. In addition to the usual carbon dioxide, benzoic acid, and biphenyl, evidences of three additional unsaturated compounds were found. Ultraviolet spectroscopy and independent synthesis disclosed the presence of 1',4',1",4"-tetrahydro-p-quaterphenyl (II) and 1,4 dihydrobiphenyl (III).



I



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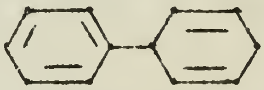

III

There was also evidence for 1,2-dihydrobiphenyl.

It is worthwhile to note the effect of different sources of phenyl radicals upon the products. In addition to benzoyl peroxide, such sources as diazonium salts (8), iodosobenzenedibenzoate $[\text{Ø}I(OCO\text{Ø})_2]$ (9), lead tetrabenzoate (10), and phenyl-3,3-dimethyltriazene $(\text{Ø}-N{=}N-N(CH_3)_2)$ (6) have been used to provide phenyl radicals. In these cases the products and isomer distributions have been in very close agreement, indicating the probability of the same mechanism being operative in all cases.

Also of interest is the fact that the isomeric distribution of diaryls usually corresponds to predictions based on such theoretical calculations as free valency and localization energy. The only reported deviation from this is in the phenylation of quinoline (11).

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NAPHTHALENE

The arylation of naphthalene seems to proceed in a manner similar to that of benzene, with an important difference attributed to the greater reactivity of the polynuclear compound. From the decomposition of benzoyl peroxide in naphthalene (12) were obtained the following products:

Table II

Product	Mean Yield (moles/mole peroxide) 85°	100°
Free benzoic acid	1.12	0.99
Naphthols	0.32	0.24
Benzoic acid from esters	0.55	0.45
Phenylnaphthalenes	0.20	0.44
Dinaphthyls	0.29	0.23
Peroxide not accounted for	0.06	0.06

The isomeric naphthyl benzoates were hydrolyzed to naphthols and benzoic acid. In addition to the expected phenyl naphthalenes, large amounts of dinaphthyls were also produced. The isomeric composition of these products was determined by infrared spectroscopy. Very little polyphenylation was found, and no benzene could be detected.

Table III

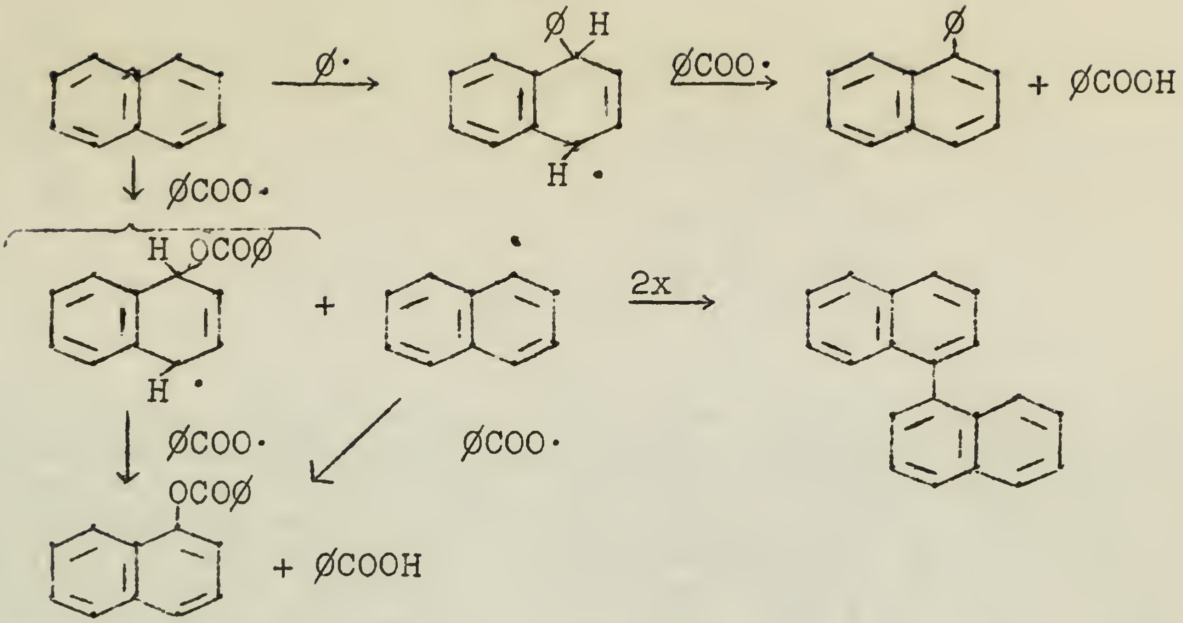
Mean Composition (%)

		1-	2-	
Naphthols	(85°)	72.9	27.1	
	(100°)	68.2	31.8	
Phenylnaphthalenes	(85°)	82.0	18.0	
	(100°)	79.7	20.3	
		1,1'	1,2'	2,2'
Dinaphthyls	(85°)	54	42	4
	(100°)	54	42	4

The formation of phenylnaphthalene probably proceeds by the same mechanism as is operative with simple aromatic systems. The esters doubtless arise similarly by the addition of benzoyloxy radical to naphthalene. This does not occur in the benzene system which is less reactive by a factor of 22 (2, 13).

In the decomposition of the benzoyl peroxide, the radical first formed is the benzoyloxy radical; this may either decompose to give CO_2 and a phenyl radical, or may add to the solvent directly. Naphthalene is reactive enough so that addition may compete with decarboxylation. Another path is apparently available to the benzoyloxy radical: that of abstraction of a hydrogen atom from the substrate to yield a naphthyl radical. Presence of the latter is suggested to account for the production of dinaphthyls. That the abstracting species is the benzoyloxy and not the phenyl radical is indicated by the absence of benzene and the presence of a large amount of benzoic acid in the product. Substitution is energetically more favored, relative to abstraction, for the phenyl radical.

On the basis of this evidence, a tentative flow diagram might be formulated:



From the distribution of isomers of the naphthols, phenylnaphthalenes, and dinaphthyls, it is seen that the 1-position is more reactive than the 2-position for both substitution and hydrogen abstraction. Higher temperatures increase phenylation by favoring decarboxylation of the benzoyloxy radical.

When isomeric nitrobenzoyl peroxides are used, the major products are naphthylnitrobenzoates with small amounts of dinaphthyls. There is no arylation.

From the decomposition of diazonium salts in acetone solutions of naphthalene (14), similar quantitative data are available concerning the distribution of isomers of phenylnaphthalenes. In this case, only aryl radicals are produced.

$$2ArN_2^{\oplus} + Zn \longrightarrow 2Ar\cdot + 2N_2 + Zn^{+2}$$

The salts used were the fluoborate (ArN_2BF_4) and zincichloride [$(ArN_2)_2ZnCl_4$].

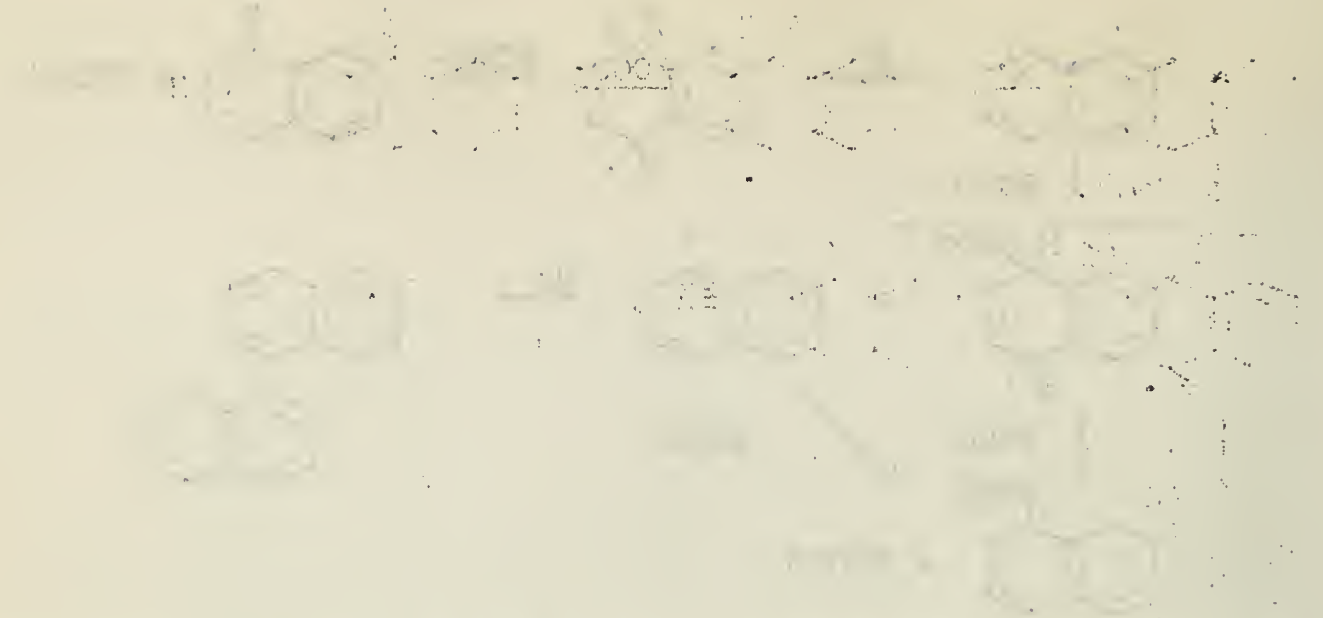
Table IV

R of p-$RC_6H_4\cdot$	1- (%)	2- (%)
NO_2	83.3 , 83.1	16.7 , 16.9
H	80.7 , 80.0	19.3 , 20.0
NHCOMe	77.0 , 76.5	23.0 , 23.5
OMe	74.1 , 73.5	25.9 , 26.5

Here again approximately the same ratio of isomers is found, there being a slight variation depending upon the substitution of the attacking radical. If similarities with electrophilic aromatic substitution are considered (1-position has the greatest electron density), it is seen that the attacking radicals have the effect on the product distribution that would be expected. Too few figures are available for a Hammett correlation, but it appears that the system might be amenable to this treatment.

ANTHRACENE

Anthracene has also been subjected to product analysis, yielding evidence for the addition-type mechanism in this aromatic system. As above, diazonium salts were decomposed with zinc in an acetone solution of anthracene (15). Isolated were 9,10-diphenylanthracene (IV) and 9,9',10,10'-tetrahydro-10,10'-diphenyl-9,9'dianthryl (V) in



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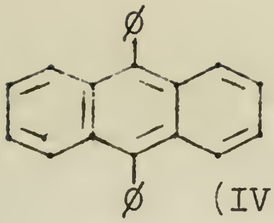
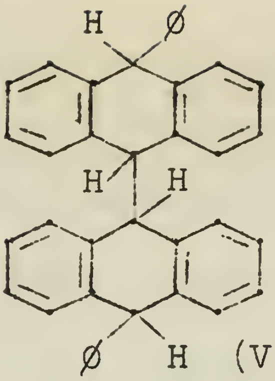
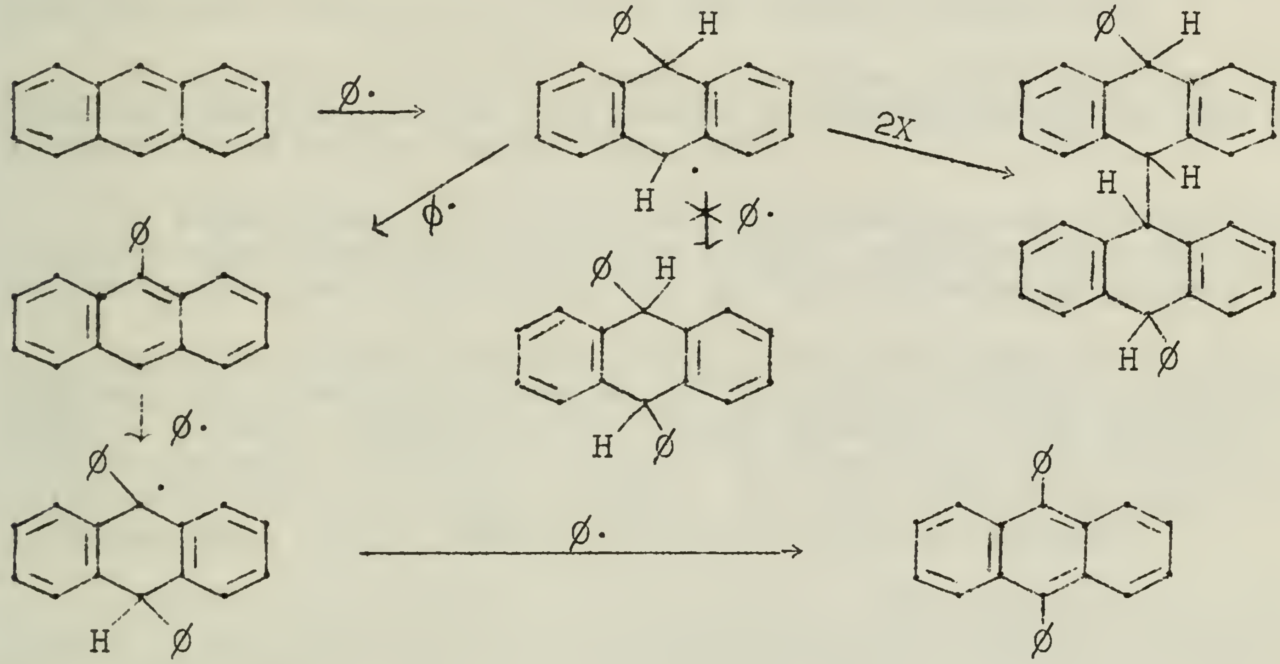

(IV)


(V)

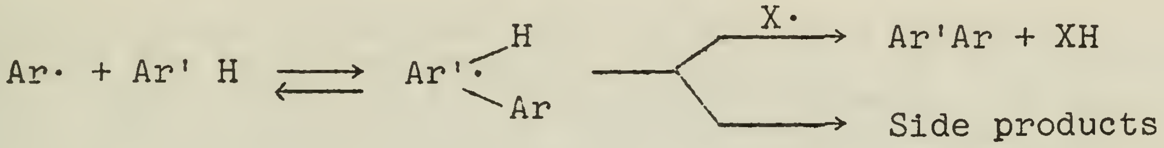
11 and 12% yields, respectively. After the addition step, if the intermediate does not dimerize, the aromatic system is regenerated. This was demonstrated by a control which proved that 9,10-dihydro-9,10-diphenylanthracene was not dehydrogenated by phenyl radicals under the conditions of the reaction. 9-Phenylanthracene must be more reactive than the parent compound toward phenylation, as this product was not isolated from the reaction mixture. The following scheme should represent the reaction:



ISOTOPE EFFECTS

With the results of homolytic aromatic substitution now outlined, we can turn to a consideration of the information gained from the study of isotope effects. These provide the strongest support for the addition mechanism. Consider first the three possible reaction paths earlier suggested. Unless there is very little bond breaking leading to the transition state, it would be expected that the first two paths should exhibit a fairly large isotope effect. For further clarification of this matter, the Hammond postulate (16) proves useful. Only for a very reactive radical would the transition state be expected to resemble the starting material, and thus involve a minimum of bond breaking. In the cases considered here, the aryl radicals are not exceedingly reactive. The reaction then would have proceeded some distance along the reaction coordinate, with some amount of carbon-hydrogen bond scission before reaching the transition state. Since the relative magnitude of the isotope effect corresponds to the amount of bond breaking, a substantial effect could be noted in the first two cases by analysis of either the product or unreacted starting material.

In the third scheme, however, the carbon-hydrogen bond is but little deformed in the addition step. If this is assumed to be rate controlling (see below), no isotope effect would be expected. However, Eliel (18) has pointed out how an isotope effect might arise in this case by considering the reaction scheme as follows:



If either reversibility of the first step or the side reaction competes with abstraction of the hydrogen atom, an isotope effect will be observed. If the first step is reversible, the isotope effect will be detected by analysis of the recovered starting material. Isotopic distribution in the product provides the key to the second cause of the isotope effect. In either case, the intermediate formed by the addition of the radical to the aromatic nucleus at a position bearing hydrogen will be converted to product in preference to the intermediate bearing a deuterium atom at the carbon-carbon bond.

Yet another source of a small isotope effect might be radical hyperconjugation (19) or the change in hybridization of the carbon-hydrogen bond at the carbon attacked.

In experiments that have been performed in an attempt to discern isotope effects in these radical substitution reactions, evidence has been found both for and against such phenomena.

Tritium-labeled dinitrobenzene was substituted with phenyl radicals from benzoyl peroxide in the work of Price and Convery (22), with no kinetic isotope effect being detected. The purified 2,4-dinitrobiphenyl (16%) was assayed, the radioactivity found being that calculated for no isotope effect. On this basis, the authors claim establishment of the radical complex reaction sequence.

After a consideration of Melander's (26) equation for the isotope effect in the similar case of electrophilic aromatic substitution, the above results must be pronounced inconclusive (23). The fraction of the original tritium found in theproduct is shown to be not only a function of theisotope effect, but of the extent of reaction. With tritium present in trace amounts in molecules of an aromatic species containing _n_ symmetrical positions for which substitution is possible, three different reactions may occur in the mixture of RH_n and $RH_{n-1}T$:

$$RH_n + X^{\oplus} \xrightarrow{nk_H} RH_{n-1}X + H^{\oplus}$$

$$RH_{n-1}T + X^{\oplus} \begin{cases} \xrightarrow{(n-1)k_H} RH_{n-2}TX + H^{\oplus} \\ \xrightarrow{k_T} RH_{n-1}X + T^{\oplus} \end{cases}$$

If the concentrations of RH_n and $RH_{n-1}T$ are given as $\underline{i}$ and $\underline{a}$, respectively, the initial concentrations are $\underline{i}_o$ and $\underline{a}_o$. β is k_T/k_H, $\underline{x}$ is the extent of reaction $(\underline{i}_o-\underline{i})/\underline{i}_o$, and the specific activity $\underline{y}$ is the fraction of a certain molecular species containing tritium: $\underline{y}_o = \underline{a}_o/\underline{i}_o$. By writing a ratio of the rates of disappearance of the

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two aromatic reactants, integrating, and making appropriate substitutions, the following equation is obtained:

$$\frac{y}{y_0} = \frac{n-1}{\beta+n-1} \cdot \frac{a_0-a}{a_0} \cdot \frac{i_0}{i_0-i} = \frac{n-1}{\beta+n-1} \cdot \frac{1}{x} \left[1-(1-x)^{\frac{\beta+n-1}{n}}\right] = f(x,\beta)$$

The fraction of tritium retained, $f(x,\beta)$, is a function of the isotope effect and the amount of reaction. Thus with low concentration of tritium, high conversion is necessary for detection of an isotope effect. With a large excess of substrate containing a high concentration of tritium (or deuterium), the equation reduces to $y/y_0 = (n-1)/(\beta+n-1)$. Sample calculations using the derived equation indicate that for an isotope effect of two and a conversion of 16%, the fraction of tritium retained in the product is 0.508. With no isotope effect, exactly half the original amount is obtained. The increase is only 1.6%, well within the experimental error of 3.1%.

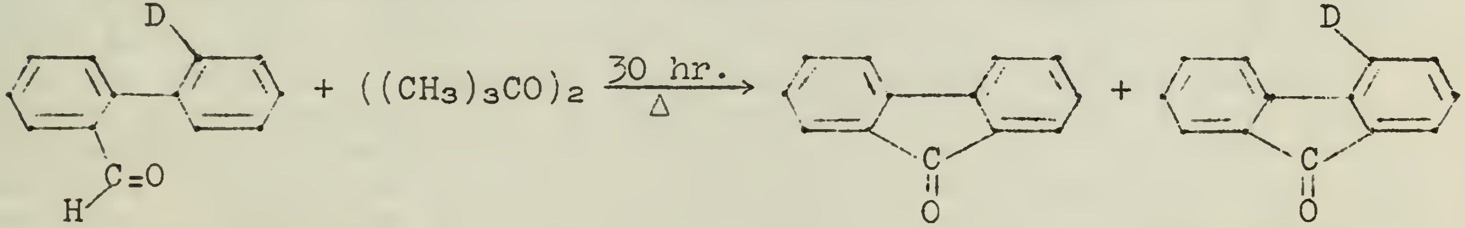
In further work, Convery and Price (24) attempted to overcome this drawback. They could not obtain high isotope concentration, and high conversion of starting material resulted in polysubstitution, making isolation of the dinitrobiphenyl impractical. The method of analysis chosen was to recover the unreacted dinitrobenzene from the reaction mixture after 75% conversion. They found the tritium content of starting material and that recovered to be very close, again indicating no isotope effect.

The assumption is made that the addition is the rate controlling step, and competition by side reactions and reversibility of the addition are not considered. If the formation of side products competes with hydrogen abstraction, an isotope effect would be manifested in the formation of the diaryl. However, unless the reversal of the addition step also competes, the isotope effect will not be detected by analysis of the starting material.

Similar results were obtained by Sheppard (21) who found no tritium isotope effect by attacking benzene-t with benzoyl peroxide.

The Russian workers (25), operating on monodeuterobenzenes, found the retention of deuterium in biphenyls to be independent of concentration of peroxide and the temperature (isotope effects decrease with increasing temperature (1)). The amount of the heavier isotope found in the product (low yield) was even less than would be expected with no isotope effect. From these data, the authors conclude that no isotope effect is involved.

In the cyclization of 2-(2-deuteriophenyl)-benzaldehyde,



(low yield)

Denney and Klemchuk (20) found an isotope effect of 1.38 in the formation of fluorenone. The decomposition of 2-(2-deuteriophenyl)-benzoyl peroxide resulted in a value of 1.32 for k_H/k_D.

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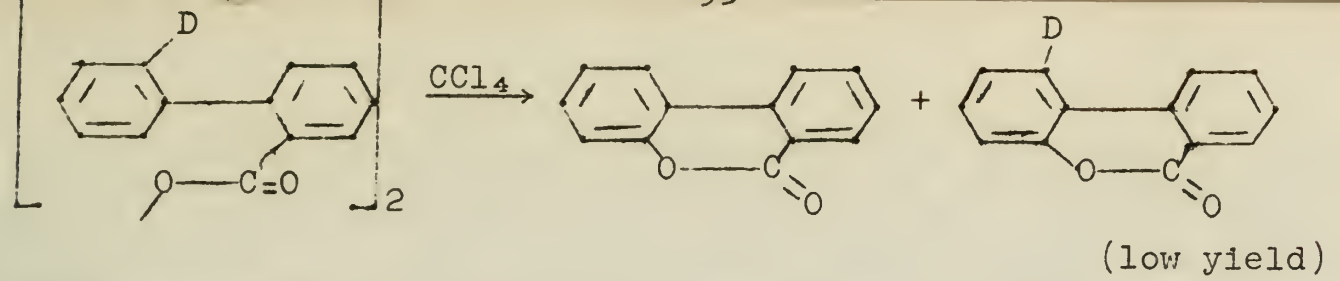


On the basis of this evidence, the authors, in agreement with the idea of the formation of a radical complex, conclude that the intermediate reverts back to starting material or a π-complex at a rate competing with that of hydrogen abstraction. They overlook the competition of the step leading to side products. However, as Eliel (18) later pointed out, the appearance of an isotope effect does not necessitate reversibility of the addition step.

In the latest published work on this subject, Eliel, Welvart, and Wilen (18) have found unequivocal isotope effects in the arylation and alkylation of benzene-d by decomposing diaroyl and diacyl peroxides in the solvent at 78°.

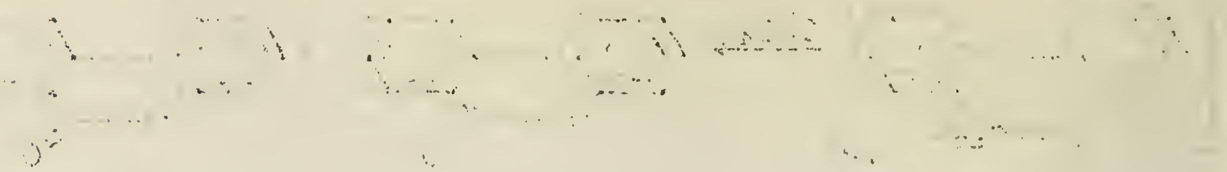
Table VII

Radical	$\frac{\text{moles } C_6H_5D}{\text{moles } (RCOO)_2}$	Isotopic Purity C_6H_5D,%	Product atom % D	 Isotope Effect
ø	42:1	93.7	7.81	1.0
	420:1	98.2	9.10	2.6
p-$CH_3C_6H_4$	50:1	97.9	7.61	2.9
p-$CH_3OC_6H_4$	50:1	96.6	6.98	1.3
p-ClC_6H_4	50:1	98.5	9.80	1.7
	25:1	93.9	9.30	1.7
p-$O_2NC_6H_4$	41:1	98.5	9.13	1.0
CH_3	24:1	97.86	11.05	1.7
	615:1	98.16	11.00	1.7

Holding to the radical complex mechanism, as was pointed out above, either reversibility of the first step or formation of side products may lead to the observed isotope effect. The results of Price and Convery (24), where the recovered 2,4-dinitrobenzene-t from the reaction driven to high conversion exhibits no significant change in isotopic composition, are used as an indication that the addition step may not be reversible.

Unpublished work by Eliel and Welvart (27), recently communicated to this author, does much to clarify this mechanistic problem. The above suspicion concerning the irreversibility of the addition step has been verified. A mixture of benzene and benzene-d_6 has been p-chlorophenylated, leading to an isotope effect of about 1.5 as determined by product analysis of the p-chlorobiphenyl. They calculated from the conversion effected, that the recovered starting material should have increased 0.7% in benzene-d_6 if the isotope effect were entirely due to competition of reversal of the first step with preferential abstraction of hydrogen over deuterium atoms from the intermediate. Within the limits of experimental error of ±0.1%, there was absolutely no change in composition of the solvent recovered, indicating no reversal.

A second discovery was that the isotope effect as determined from product composition depends greatly on the reaction conditions. In the phenylation of benzene-d in very dilute solution, values of the



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isotope effect varied from a little over 2 to more than 6, if precautions were taken to prevent oxidation of the 1,4-dihydrobiphenyl formed (see results of De Tar above). Thus it seems that, at least in dilute solution, the high isotope effect arises through the disproportionation of the arylcyclohexadienyl radical to biphenyl and dihydrobiphenyl. Hydrogen would be preferentially removed from the biphenyl and retained by the dihydrobiphenyl. If the hydrogen enriched dihydrobiphenyl is reoxidized to biphenyl, the isotope effect, as measured by the deuterium content of the product biphenyl, will be decreased. On this basis, the biphenyl derived from dihydrobiphenyl should contain some $\underline{d}_2$ material. This has been experimentally verified.

On the basis of this information, while the isotope effects have been invaluable in depicting the reaction path, their magnitudes are of little significance. The intermediate radical complex formed irreversibly may undergo a number of reactions. Hydrogen may be abstracted by benzoyloxy radicals or benzoyl peroxide; two radicals may disproportionate or dimerize. Reactive coupling products may undergo further radical attack with polymeric material as the result.

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THE BENZILIC ACID REARRANGEMENT

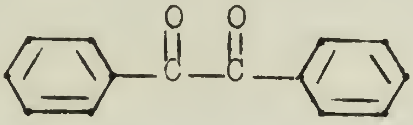
Reported by L. H. Shepherd April 16, 1959

INTRODUCTION

The benzilic acid rearrangement was one of the earliest recognized organic rearrangements, being first reported by Liebig (1) in 1838. The mechanism remained obscure for many years, but has finally been explained through the use of refined techniques as tracer studies and the kinetic isotope effect. This seminar will cover the most enlightening work up to the present.

The reaction is usually carried out by means of aqueous alcoholic alkali hydroxide solution (1,2,3,4). However, the transformation of benzil (I) to benzilic acid (II) is known to occur in aqueous solution in the absence of base (5), and in certain basic media in the absence of water (6,7). For example, Evans and Dehn (7) placed a lump of potassium hydroxide weighing 1.4 g. in absolute ether with 5.4 g. of benzil. The mixture was shaken occasionally over a period of four days at the end of which 5.4 g. of a light yellow, powdery solid was isolated. The salt on acidification gave benzilic acid.

(I)



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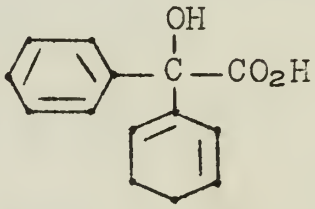
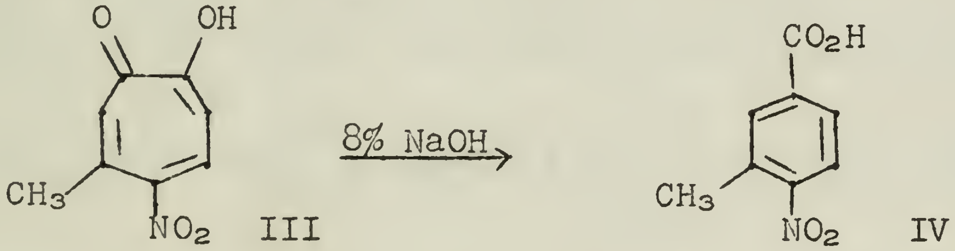


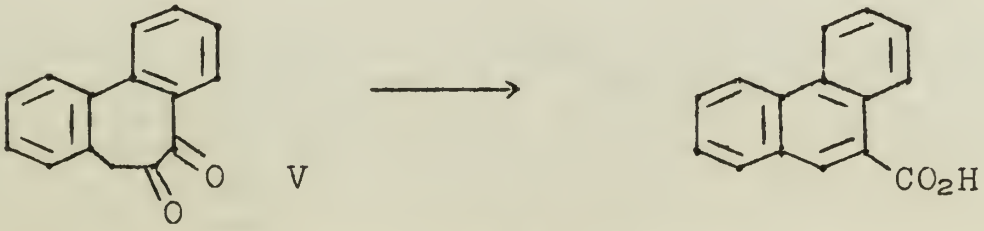
The benzil-type base-induced reaction is not limited to benzil, but has been realized in various α-diketone systems. Howorth and Jefferies (8) have carried out this rearrangement using 2-hydroxy-6-methyl-5-nitro-2,4,6-cycloheptatriene 1-one (γ-nitro-β-methyltropolone) (III) forming 3 methyl-4-nitrobenzoic acid (IV). Also,



III

IV

dibenzotropolone (V) has been reported to undergo a similar reaction with potassium hydroxide yielding 9-phenanthrenecarboxylic acid (VI).



V

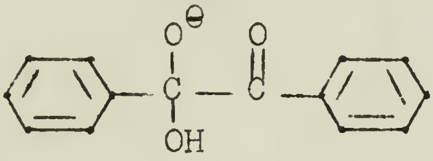
VII

The reaction has been studied in the D-homosteroid series and will be considered later in the paper.

MECHANISM AND KINETICS

Until recently it was believed that the reaction was induced specifically by hydroxide ion and not subject to catalysis by other bases. This is indicated by the failure of sodium ethoxide to induce the reaction (9,10). Westheimer has reported that phenylate and ortho-chlorophenylate ions have no effect on the rate of the reaction in aqueous ethanol solution, indicating that only hydroxide ions brought about the conversion of benzil to benzilic acid.

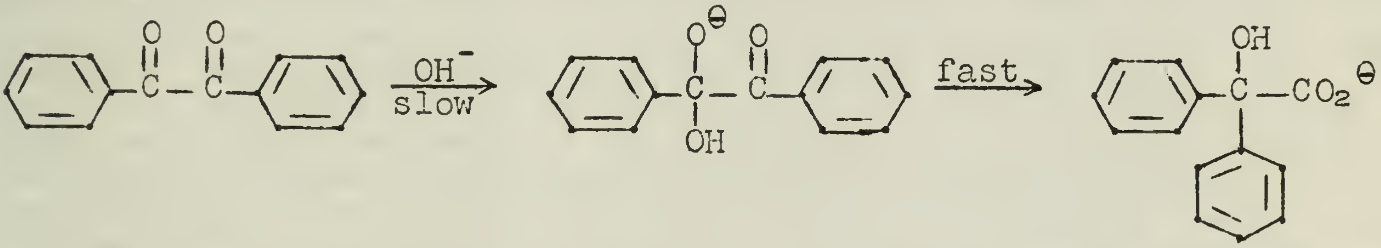
A kinetic study also made by Westheimer showed the reaction to be second order: first order in hydroxide ion and first order in benzil (11,12). These findings could be explained most readily on the basis of the original assumption made by Ingold (13), that the reaction proceeded through an intermediate ion VII.



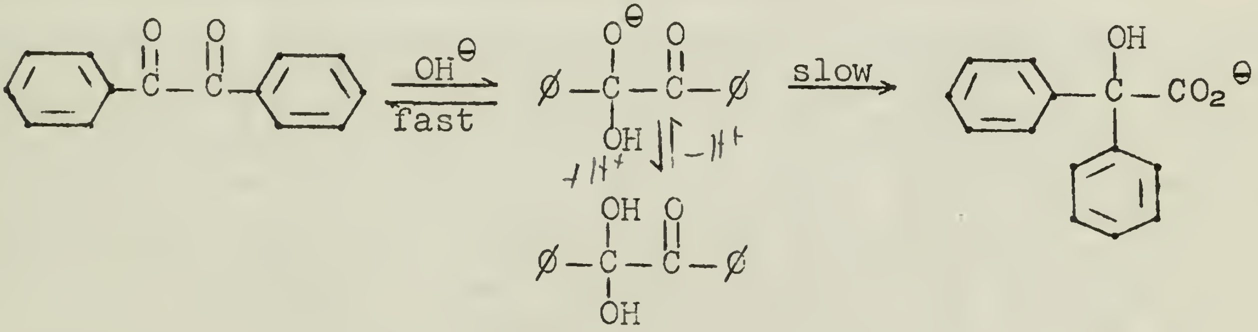
VII

There are two different mechanisms which would follow second-order kinetics and it was finally Roberts and Urey (14) who through the use of H_2O^{18}, determined the correct path. Possible mechanisms kinetically indistinguishable and of second order are:

a) a slow reaction between one molecule of benzil and one hydroxide ion followed by rapid rearrangement of the ion



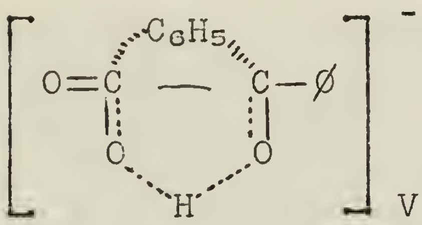
b) a rapid reversible addition of hydroxide ion which is followed by the slower, rate-controlling rearrangement



By calculating the percent exchange of benzil carbonyl oxygen in a water solution containing H_2O^{18}, Roberts and Urey showed that carbonyl oxygen exchange occurs in neutral solution, but much faster in the presence of hydroxide ions, and on this basis mechanism a) could be excluded, for this would not allow for any oxygen exchange before rearrangement. This also showed that the rate-controlling step was the one where rearrangement occurred. Below is a short table of the results of the experiments conducted by Roberts and Urey.

Experiment	NaOH	Time (min.)	% Carbonyl Oxygen Exchange
1	-	2.5	16 ± 7
2	-	4	43 ± 6
3	.02*N*	4	100 ± 6
4	.02*N*	4	102 ± 6

A transition state (VIII) has been suggested by Clark, Hendley, and Neville (15) which would have the negative charge evenly distributed over the phenyl group, two carbon atoms, two oxygen atoms as well as the hydrogen atom which is being transferred from a hydroxyl oxygen to a carbonyl oxygen. They suggest that this



VIII

transition state accounts for the inability of other bases (methoxide, ethoxide, phenolate) to induce the reaction as these groups would not be expected to permit migration of a group coincident with phenyl migration. However, Doering and Urban (16) have found that boiling anhydrous methanolic sodium methoxide reacts with benzil to yield methyl benzilate and also small amounts of benzoin, benzilic acid and benzaldehyde. When solid potassium *t*-butoxide was dissolved in benzene, and the solution was treated with benzil, *t*-butyl benzilate was obtained in 90% yield. When *t*-butyl alcohol and potassium *t*-butoxide were used, the reaction was found to exhibit second order kinetics, and *t*-butyl benzilate was isolated in 76% yield. By contrast, sodium ethoxide is unsatisfactory for the production of ethyl benzilate and leads to the formation of several by-products (17,18,19) because of the Meerwein-Ponndorf-Verley-Oppenauer equilibrium. From the work reported above, Doering and Urban concluded that it is not a necessary condition for the benzilic rearrangement that, simultaneous with the carbon rearrangement there be an intramolecular transfer of a proton.

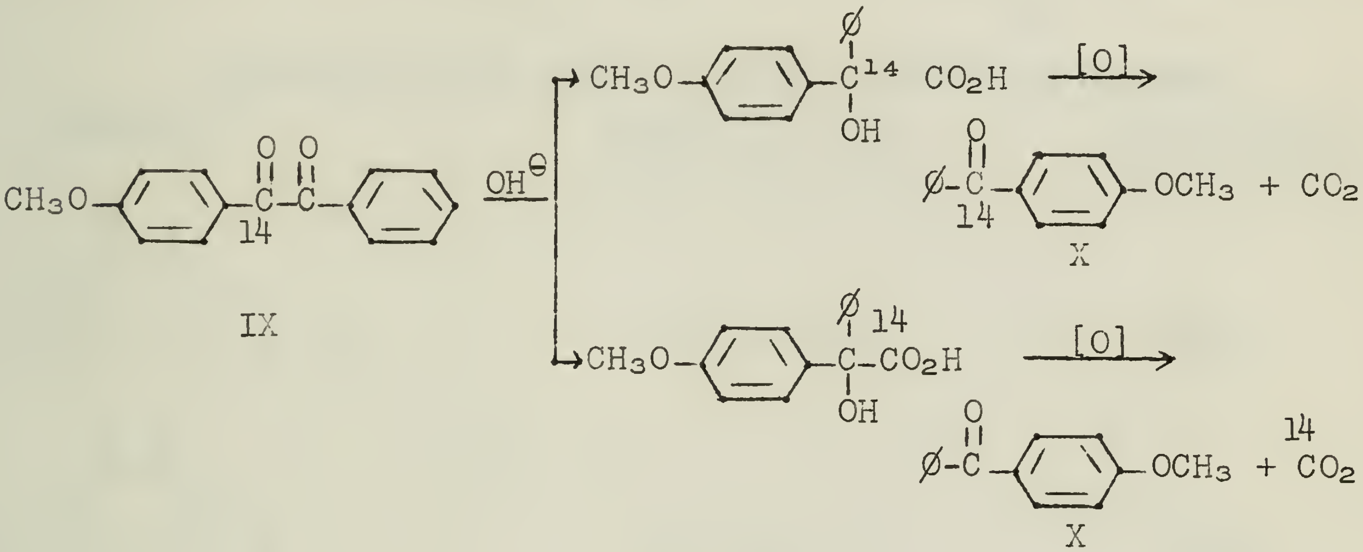
In order to test whether the concerted proton transfer (VIII) occurs in the reaction with hydroxide ion as proposed by Neville and his coworkers (15), Hine and Haworth (20) have conducted a series of kinetic experiments in which the rate of the benzil-benzilic acid transformation was determined in H_2O and D_2O. If the hydrogen atom is transferred from the hydroxyl oxygen to the carbonyl oxygen in the rate-controlling step there should be a marked decrease in the reaction rate when D_2O is used instead of H_2O. The reaction was carried out in 66% aqueous dioxane and was found to exhibit second-order kinetics. From the data in the following table, it is seen that the rearrangement actually proceeds about 85% faster with $NaOD-D_2O$ than with $NaOH-H_2O$. This increase in rate is attributed to the greater basicity of deuteroxide ion in deuterium oxide solution compared with hydroxide ion in H_2O (22,23,24). The fact that there is only a relatively small difference in the reactions run in H_2O and D_2O led Hine to suggest that the mechanism for simultaneous phenyl group migration and proton transfer is extremely improbable.

Reaction of Benzil with Alkali in Dioxane: H_2O (2:1)

Temp, °C	Water Used	10^5k, l. mole^{-1} sec^{-1}
50.0	H_2O	10.04 ± 0.35
50.0	H_2O	9.98 ± .32
50.6	D_2O	18.78 ± .52
49.5	H_2O	8.11 ± .10
49.5	D_2O	14.91 ± .08
49.8	H_2O	8.67 ± .02
49.8	D_2O	16.22 ± .02

MIGRATION TENDENCIES IN SUBSTITUTED BENZILS

An examination of relative migratory tendencies of substituted phenyl groups provided some additional important information on the mechanism of the benzilic acid rearrangement. Thus, Roberts, Smith and Lee (25,30) measured the migration ratio of the p-methoxyphenyl to the phenyl group by use of a C^{14}-labelled carbonyl group next to the substituted phenyl ring in p-methoxybenzil (IX). The benzilic acid obtained was oxidized to the corresponding p-methoxybenzophenone.

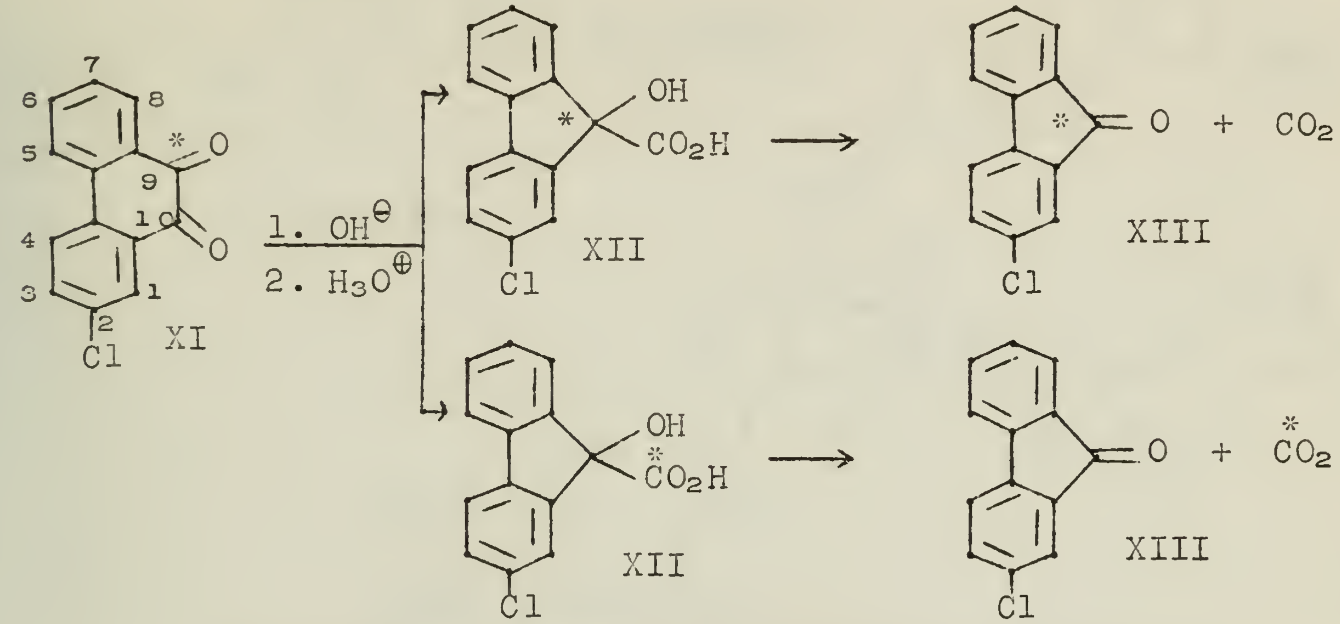


Analysis of the final oxidation product (X) by radiochemical methods showed the ratio of pheny- to p-methoxylphenyl-group migration to be about 2:1. Migration ratios for benzils substituted in one ring were also obtained by Clark Hendley and Neville (15) using tracer technique with a C^{14}-carbonyl carbon next to the unsubstituted phenyl ring, with the results indicated in the following table.

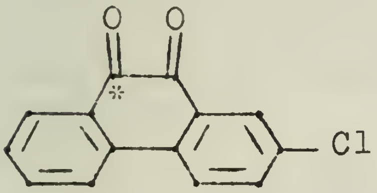
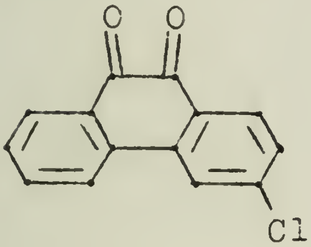
Rearrangements of $C_6H_5\overset{*}{C}OCOR$

R	% Migration R	Migration R vs. Phenyl	Adjusted Migration R	Adjusted % Migration R (For Isotope effect) (26)
p-methoxyphenyl	31.3	0.456	0.406	28.9
p-methylphenyl	38.8	0.634	0.564	36.0
p-chlorophenyl	67.2	2.05	1.82	64.6
m-chlorophenyl	81.2	4.10	3.65	78.5

The use of C^{14} isotopic labeling has been extended by Ott and Smith (27) to the alkaline rearrangement of chlorophenanthraquinones (XI) and oxidation of the acid (XII) product to the corresponding chloro-substituted fluorenone (XIII). The 9-position was labeled with C^{14}.



Migration Preferences of Chlorophenanthraquinones

Compound	Migration Ratio Subst./unsubt.	% Migration Substituted
	4.93 ± 0.23	83.1%
	2.01 ± .03	66.8%

These results are consistent with the previously discussed works (15,25,30) in that phenyl groups holding electron withdrawing substituents migrate to a greater extent than does a pheny group or a phenyl group holding electron donating substituents.

STEROSELECTIVE ASPECTS

Recently, it has been reported that the benzilic acid type rearrangement may follow a steroselective course in special systems. Georgian and Kundru (29) have utilized this reaction to transform D-homosteroids to steroids. The D-homosteroids were derived from cortisone (XIV), cortisol (XV), and Reichstein's substance S (XVI), and rearranged back to the normal steroid structure. As an example of dione formation in the D-ring, substance S will be considered. Substance S (XVI) undergoes D-ring expansion in the presence of Lewis acids to give a mixture of mono (XVIIA) and diacetates (XVIIB) which on hydrolysis followed by oxidation gives the D-homosteroid dione (XVIII).

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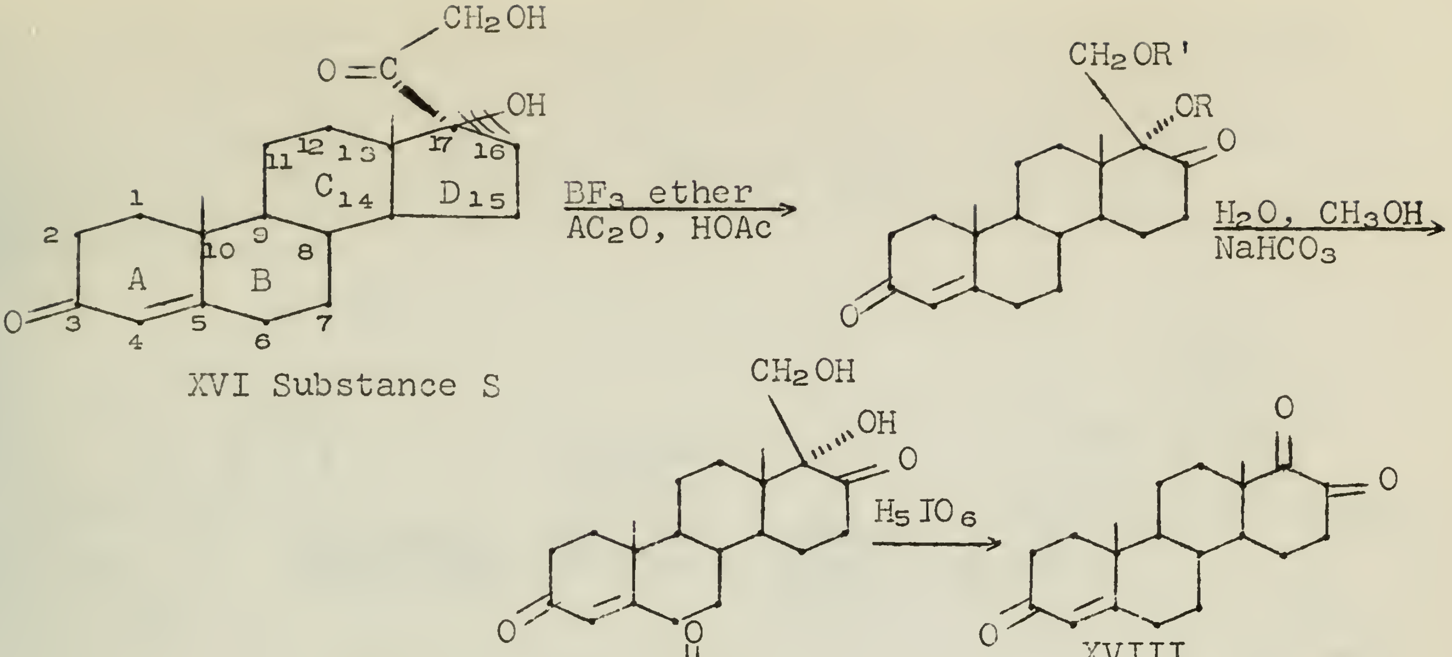


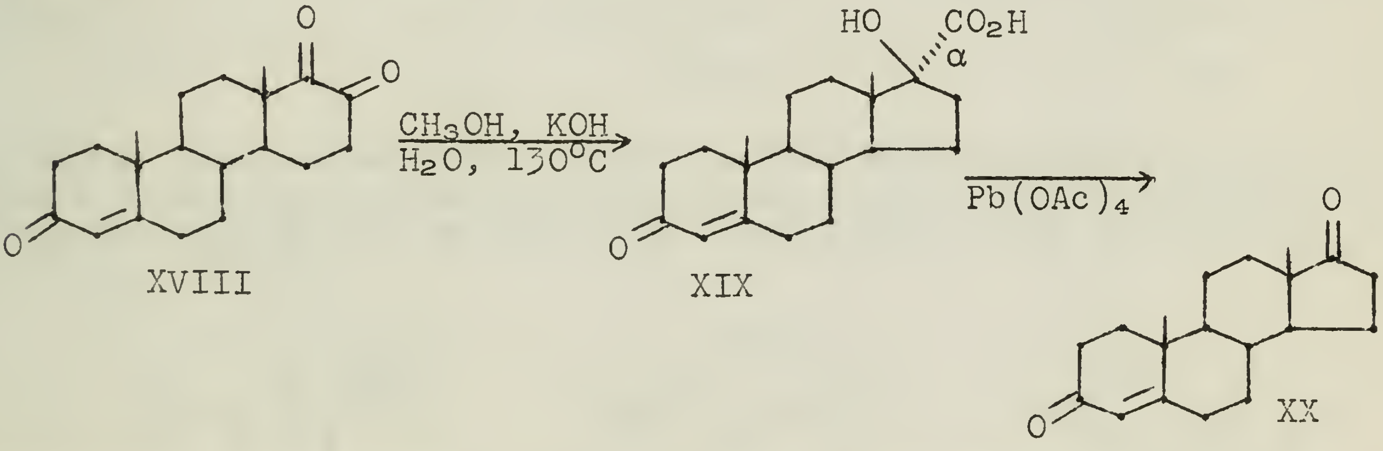
XVI Substance S

XVIII

XVIIA $R = H \quad R' = \overset{\displaystyle O}{\overset{\|}{C}}CH_3$

XVIIB $R = R' = \overset{\displaystyle O}{\overset{\|}{C}}CH_3$

Upon treatment with aqueous alcoholic base, compound XVIII is found undergo a benzilic acid rearrangement, back to the normal steroid structure, to an acidic compound (XIX) which on oxidation with lead tetraacetate was transformed into androstene-3,17-dione (XX), showing that both the carboxyl and hydroxyl group formed are in the C-17 position.

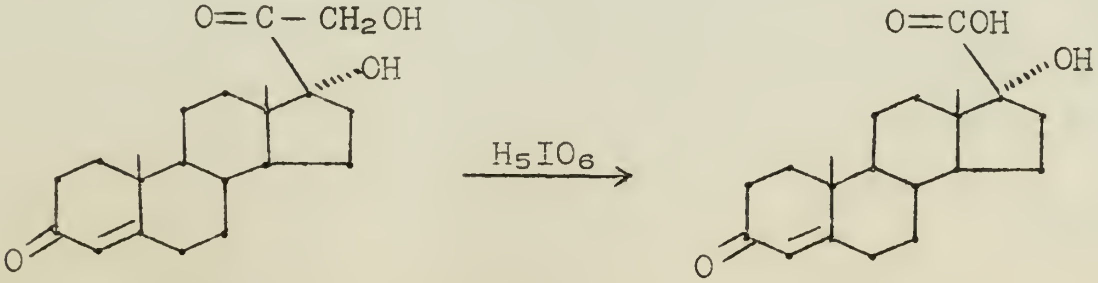


XVIII

XIX

XX

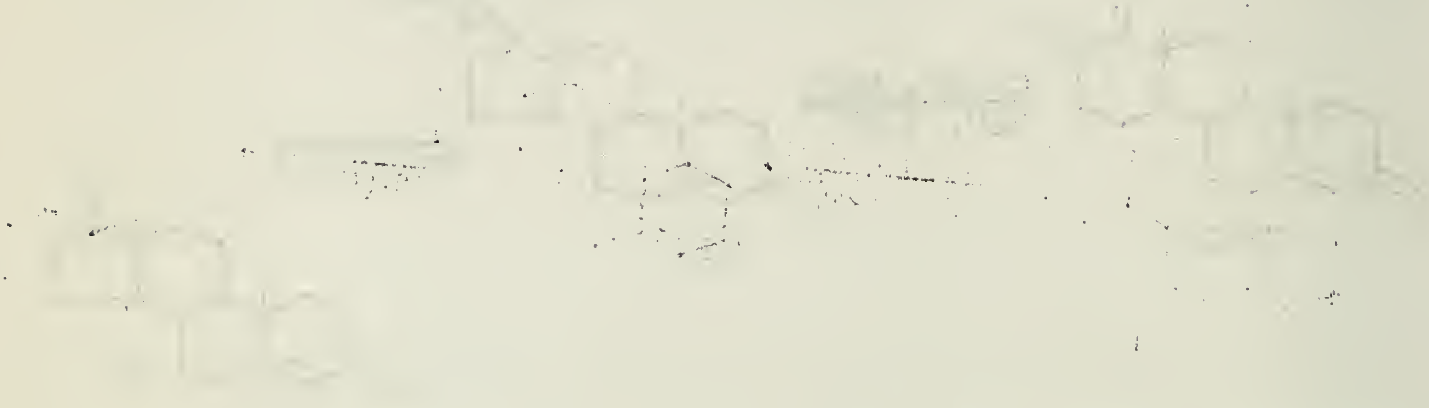
Reichstein's substance S (XVI) is known to have the C-17 hydroxyl group projecting downward (α). The rearranged acid (XIX) depressed the melting point of the 3-keto-17α-hydroxy-Δ^4-etiocholenic acid (XXI) obtained by periodate oxidation of substance S. The structure of acid (XIX) must therefore be that of a 17β-hydroxy etiocholenic acid.



XVI

XXI

[illegible]



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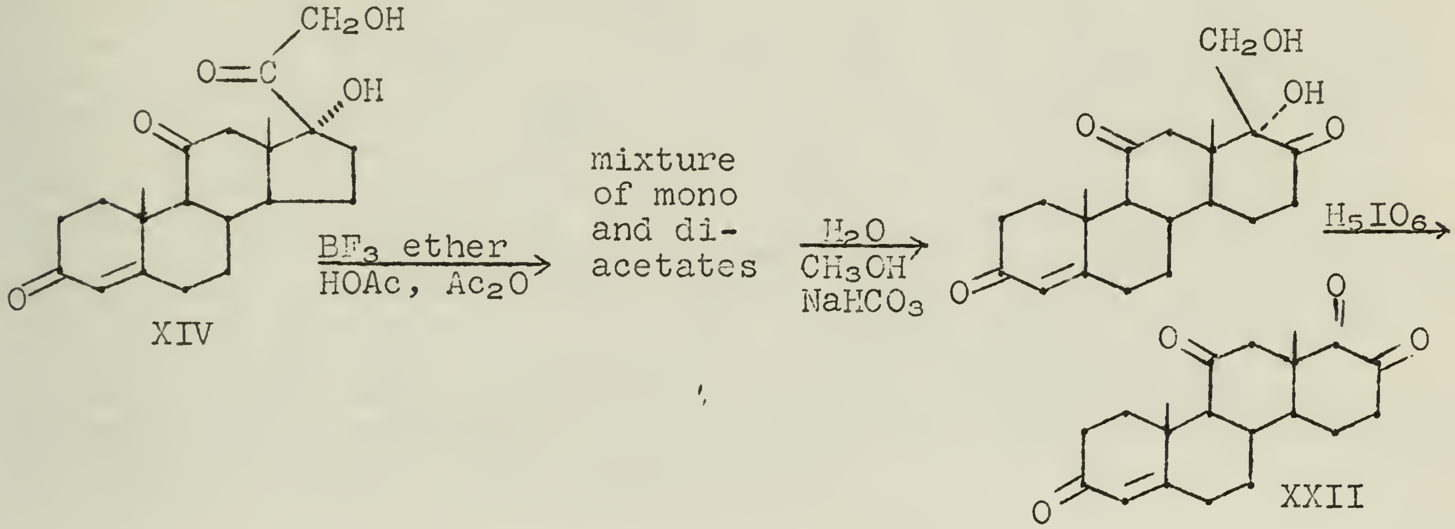
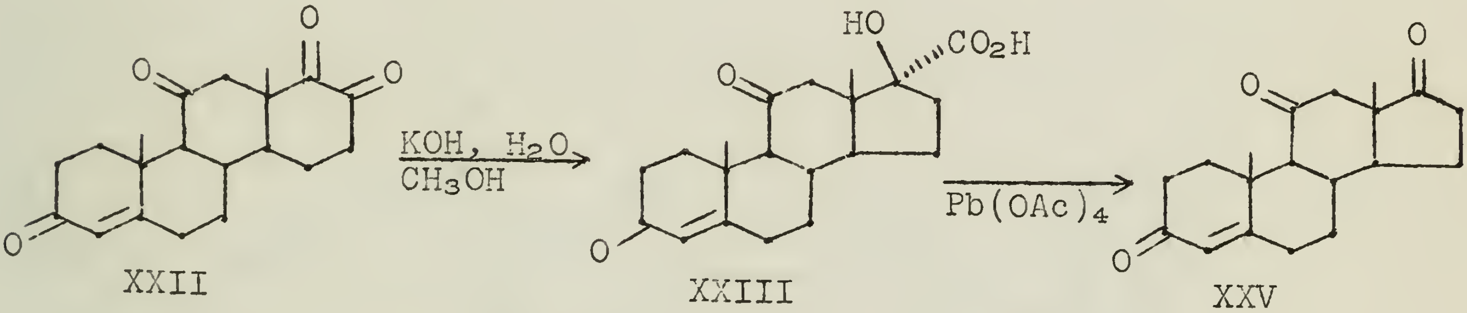
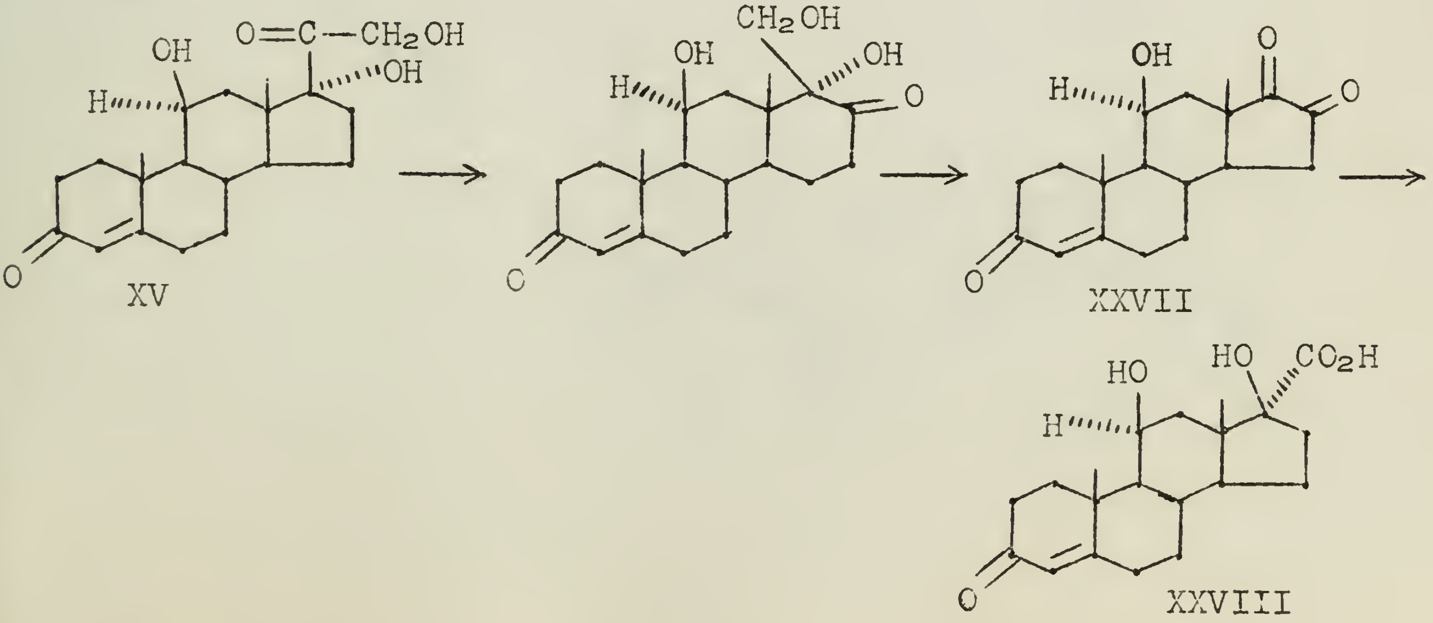
In a similar manner, the D-homodione XXII obtained from cortisone (XIV) was rearranged to a steroid acid (XXIII). This acid (XXIII) differed from the acid prepared by periodic acid oxidation of cortisone; moreover, the acid (XXIII) obtained on rearrangement of compound XXII was oxidizable to andrenosterone (XXV), thus establishing that the hydroxyl group is at the C-17 position and in the β-orientation.

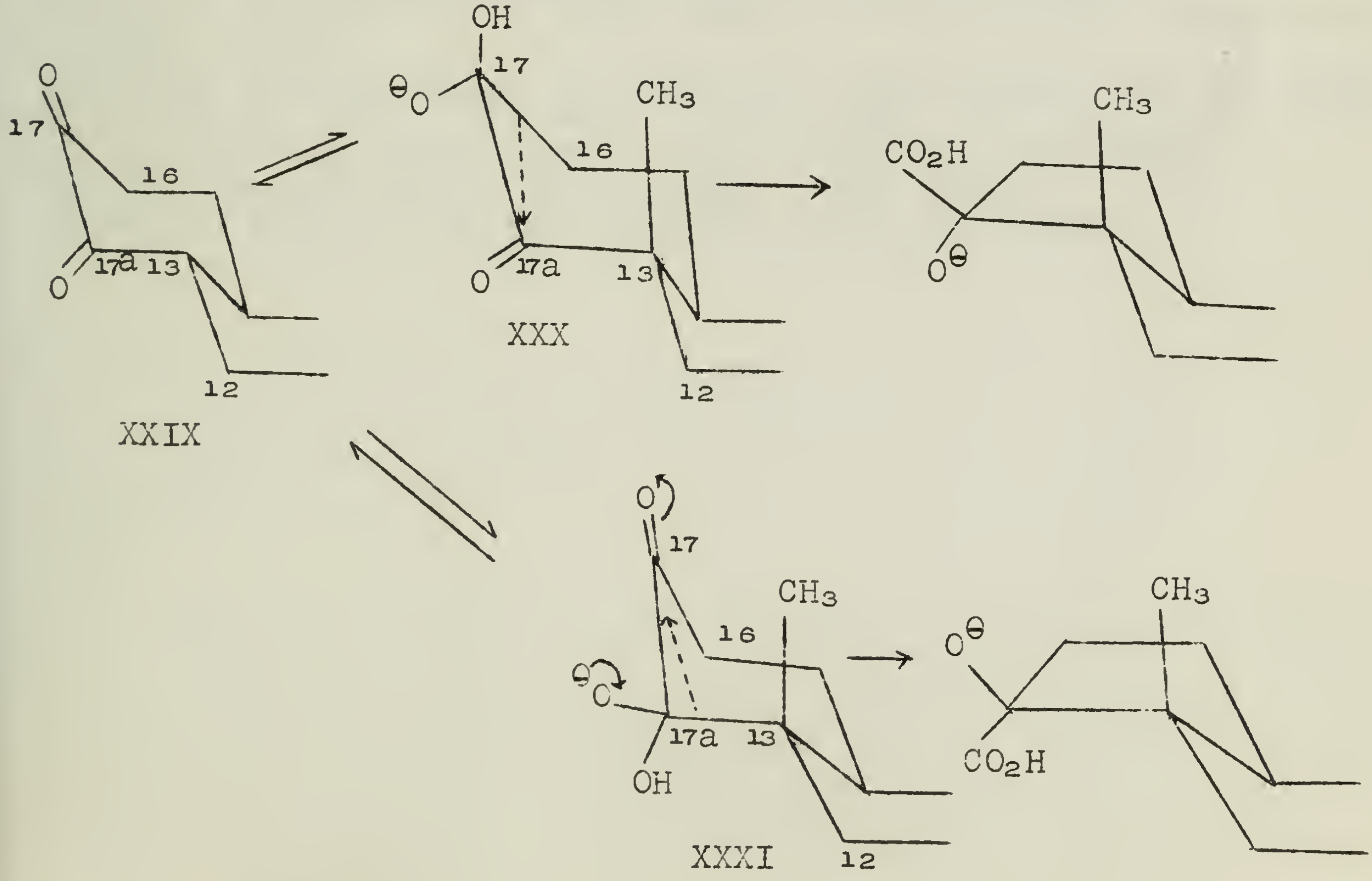




Likewise, the D-homodione (XXVII) derived from cortisol (XV) was found to undergo a stereoselective rearrangement in the presence of hydroxide ion giving an acid with a β-hydroxyl group at the C-17 position (XXVIII).



The benzilic acid rearrangement appears to have proceeded predominantly in one steric sense, that initiated by attack of the hydroxide ion on the 17a-keto group. The observed products (XIX, XXIII, XXVIII) can be explained in terms of transition state energies of the species involved. When the hydroxide ion attacks a D-homo-dione steroid (XXIX) at the C-17 position an intermediate (XXX) is formed which can theoretically undergo rearrangement. In the transition state of this intermediate it is seen that the forming of a bond between C-17a and C-16 requires that the carboxyl group being formed be near the methyl group attached to C-13, thereby causing an unfavorable condition. However, if the C-17a position is the site of attack by the base as in XXXI, this leads to a transition state in which a hydroxyl group is in the vicinity of the C-13 methyl group. Considering each transition state involved in the rearrangement of XXX and XXXI, it seems reasonable that the one involving carboxyl and methyl group interaction would require a higher activation energy than the one involving only hydroxyl and methyl group interaction. If this is true, then rearrangement of XXXI proceeds through an activated state having lower energy than the transition state of intermediate XXX and forms the experimentally observed product having the hydroxyl group in the β-orientation.



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EPOXIDATION OF CONJUGATED CARBON-CARBON DOUBLE BONDS

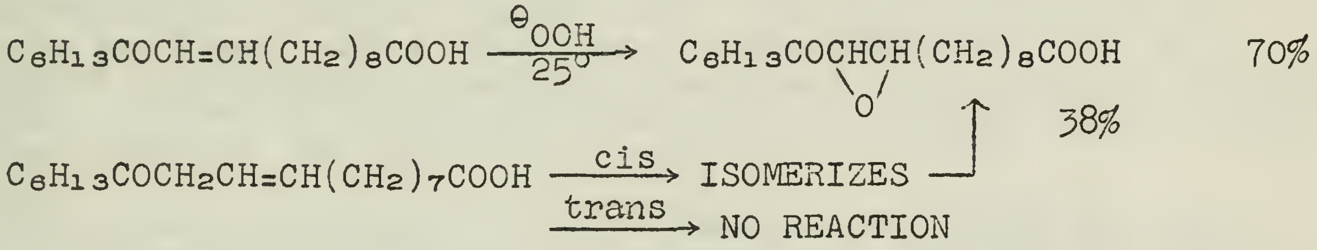
Reported by R. S. Neale April 20, 1959

INTRODUCTION

It is the writer's intention to present an indication of the methods which have been shown to be of concrete synthetic value in the epoxidation of specific types of conjugated double bonds. Mention is made of unexpected reactions, and information is presented which bears on the mechanism or limitations of a type reaction. For reviews concerning epoxidations carried out with organic peracids, the reader is referred to articles by Swern (1,2).

EPOXIDATION OF α,β-UNSATURATED KETONES

Alkaline hydrogen peroxide. The most reliable and common reagent for effecting epoxidation of α,β-unsaturated ketones is alkaline hydrogen peroxide. Weitz and Scheffer (3) showed that the reagent does not attack isolated olefinic linkages and carbonyls, dienes, or α,β-unsaturated esters and acids. For example, sorbic acid, $CH_3CH{=}CHCH{=}CHCOOH$, fails to react during treatment with the reagent at 0° for several days. An example of the use of the reagent on a preparative scale (0.333 mole) is the epoxidation (4) of keto-fatty acids:

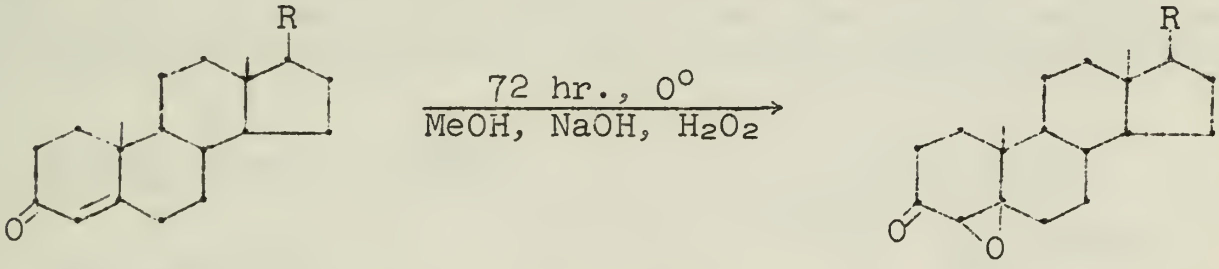


$$C_6H_{13}COCH{=}CH(CH_2)_8COOH \xrightarrow[25^\circ]{^{\ominus}OOH} C_6H_{13}CO\underset{O}{CHCH}(CH_2)_8COOH \qquad 70\%$$

$$C_6H_{13}COCH_2CH{=}CH(CH_2)_7COOH \xrightarrow{cis} \text{ISOMERIZES} \uparrow \; 38\%$$

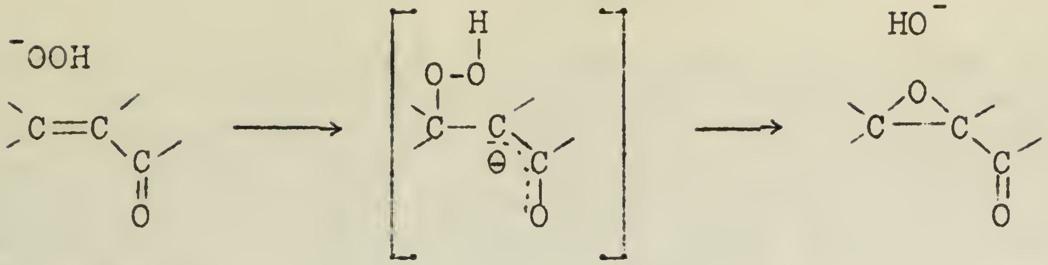
$$\xrightarrow{trans} \text{NO REACTION}$$

Representative of the reaction in steroid chemistry is the conversion (5) of Δ^4-cholestenone to 3-keto-4β,5-epoxycoprostane.

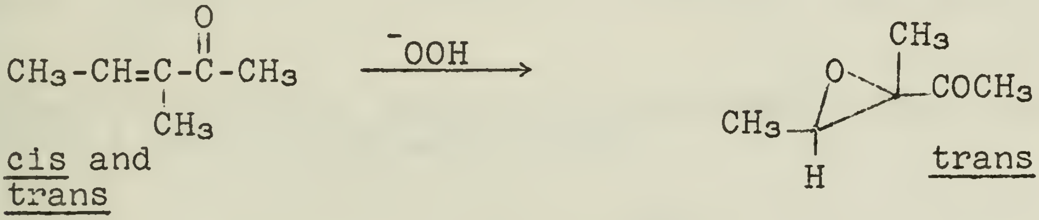


Cleavage by alkaline peroxide has been reported in certain cases (6). Some ketones are completely unreactive towards this reagent, specifically, those with unsaturated centers forced out of plane with respect to one another. House (7) has found that α-substituted-cis-benzalacetophenones can be epoxidized most conveniently according to the method of Wasserman and Aubrey (8), in which the ketone is reduced with lithium aluminum hydride, the hydroxy olefin formed is epoxidized with peracetic acid, and the ketone is regenerated with chromic anhydride in pyridine.

Mechanism of alkaline peroxide epoxidation. Kinetic studies (9) have shown that the epoxidation of α,β-unsaturated ketones is second order, first order both in ketone and in peroxide ion. This is evidence in favor of an attack on the olefin by HOO^- as shown.

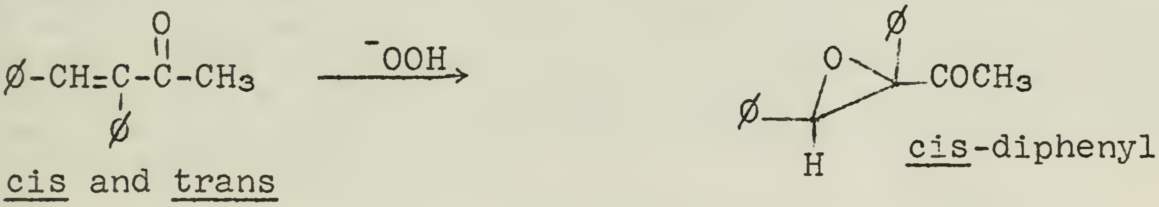


The base-catalyzed epoxidation of unhindered, unsaturated ketones lacking an α-hydrogen atom is not stereospecific (10). An olefin in which steric interactions of the cis-isomer (7) are unimportant was studied: both cis- and trans-3-methyl-3-penten-2-one yielded the trans-epoxide on treatment with alkaline peroxide. Both products had identical gas chromatograms, infrared spectra, and nearly identical physical properties. That the base-catalyzed epimerization of cis-



and trans-oxides proceeds via abstraction of the α-hydrogen atom in β-methyl-trans-benzalacetophenone oxide was shown by treating it with sodium ethoxide in deuteroethanol (10). One deuterium atom per molecule was found, and a comparison of the NMR spectra of the deuterated and starting materials showed that the α-hydrogen had been replaced. Hence, an α-hydrogen could not be tolerated in the stereochemical study of the epoxidation reaction.

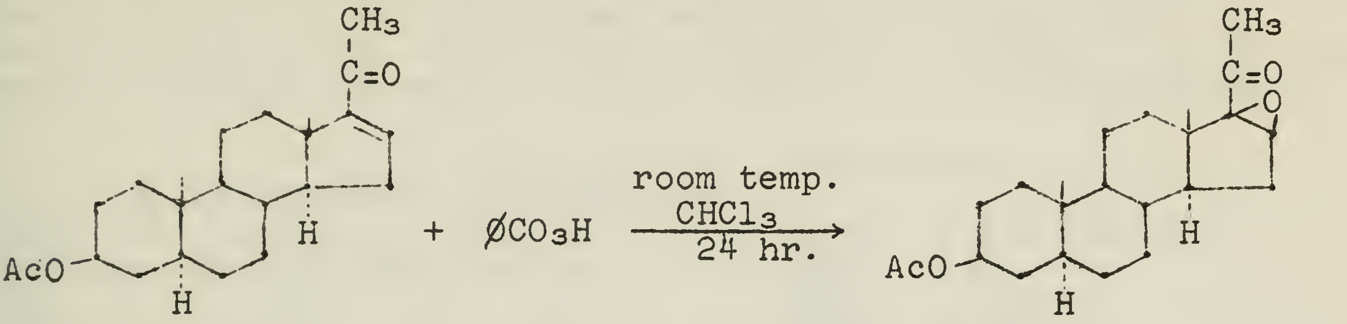
The product configuration is not determined solely by steric strain, since α-phenyl-trans-benzalacetophenone affords the slightly more strained stereoisomer with cis-phenyl groups (11,12). Zimmerman and co-workers (13) synthesized cis- and trans-α-phenylbenzalacetone, proved their configurations, produced the corresponding epoxides, and showed that treatment with alkaline peroxide yields exclusively 3,4-cis-diphenyl-3,4-epoxybutan-2-one. This is explained by assuming



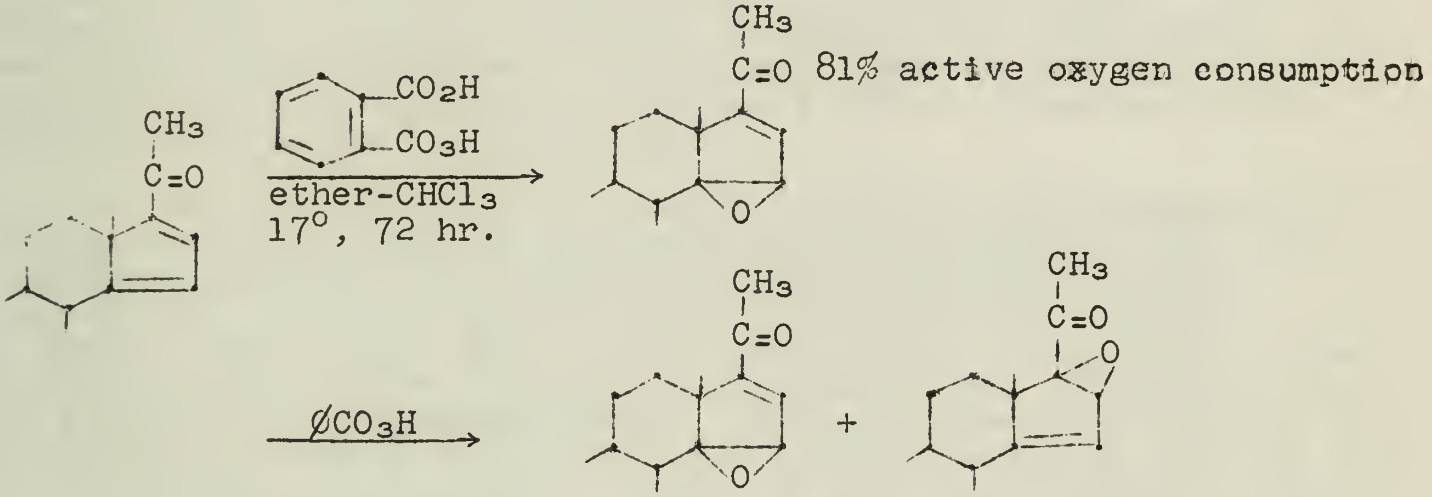
that the stabilization of the transition state is decreased by forcing the acetyl group cis to a phenyl, since the acetyl group cannot assume the planar relationship necessary for maximum orbital overlap with the epoxy oxygen and the α-carbon orbitals (coplanar with C-4 and α-phenyl C-1). When the acetyl function is trans, it can delocalize the charge more efficiently. The conclusion is drawn and further supported that alkaline epoxidation is overlap controlled and yields the product with the less hindered carbonyl group, which has the more stable transition state.

Organic peracids. The usefulness of these reagents in effecting epoxidation of conjugated ketones has been investigated. Concentrated solutions of methyl sorbate or sorbic acid when treated at 0° with perbenzoic acid (14) take up one mole of active oxygen after two days

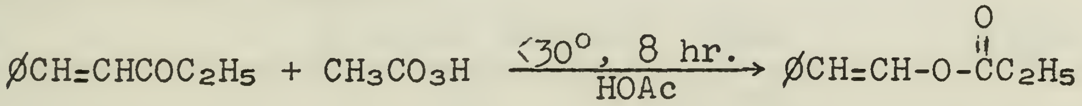
to yield the 4,5-epoxide. Although Swern (1) states that perbenzoic acid will not attack double bonds substituted with the electron withdrawing groups -COOH, -COOR, -CO, and -CHO, it has been found by Plattner, Ruzicka, Heusser, and Anglicker (15) that Δ^{16}-3β-acetoxy-5-allopregnen-20-one could be converted, using a 4 molar excess of perbenzoic acid, to 3β-acetoxy-16,17-epoxy-20-keto-5-allopregnane. One mole of active oxygen was consumed.



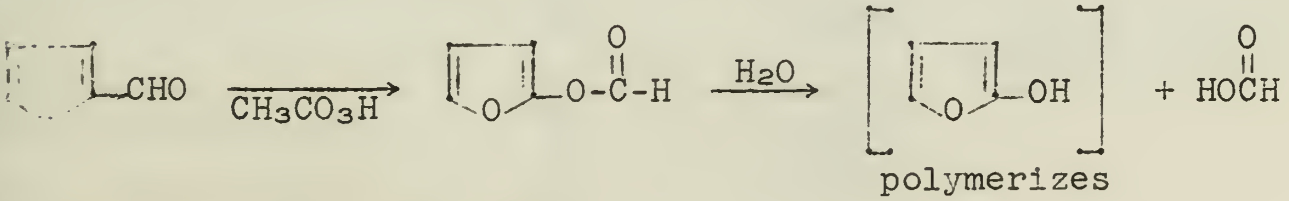
A slightly less active reagent was employed by the same workers to epoxidize a more conjugated system.



Peracetic acid has been reported (16) to lead to esters only, *via* a Baeyer-Villiger reaction. Ethyl styryl ketone, when treated for 8 hours with peracetic acid in acetic acid solution, yields styryl propionate. That the epoxide is not an intermediate was shown by synthesizing it by another route and showing that it is stable under the reaction conditions. Similarly, furfural yields as a first product furfuryl formate.



$$\phi CH{=}CHCOC_2H_5 + CH_3CO_3H \xrightarrow[HOAc]{<30^\circ,\ 8\ hr.} \phi CH{=}CH\text{-}O\text{-}\overset{O}{\overset{\|}{C}}C_2H_5$$



UNSATURATED ACIDS AND ESTERS

There have been found few methods of transforming directly an α,β-unsaturated ester or acid into the corresponding epoxide. The use of performic acid is reported to lead only to glycols (2) while alkaline hydrogen peroxide reacts only slightly, if at all. The

previously indicated action of perbenzoic acid on methyl sorbate or sorbic acid (14) demonstrates the ineffectiveness of the reagent on the carbonyl-conjugated C=C. The use of higher temperatures to increase the rate of reaction with peracids leads only to hydroxylated compounds (17,18). Compounds of the type, $R_2C=CH-O-COR$, react normally with peracids (2). Payne and Williams (19) have reported that conjugated acids can be epoxidized in reasonable yields by the sodium tungstate-catalyzed action of alkaline hydrogen peroxide on the half-neutralized acid. Only three reactions were reported. The amount of catalyst was varied from 2 to 10 mole percent. The pH was maintained between 5.5 and 4.0 by the addition of sodium hydroxide.

Acid	% free epoxy-acid	% Na salt by titration of active O
maleic	77	95
fumaric	50	86
crotonic	50	80

Conditions:

Acid: 2 equivalents
NaOH: 1 eq.
H_2O_2: 1.2 mole
Temp: 63-65°
Time: 1-4 hr.

Simple olefins were less reactive. Thus, 2-heptene after 6 hours showed only 66% reaction by titration for active oxygen. The function of the inorganic catalyst is unknown, but the authors hint that sodium tungstate forms an inorganic peracid by reaction with H_2O_2 which effects epoxidation through a cyclic transition state involving the peracid and the olefin.

The only method which has proved useful for the epoxidation of conjugated esters involves (20) treatment of the ester with trifluoroperacetic acid in methylene chloride-disodium phosphate suspension. Yields up to 84% are obtained with this catalyst, which is weakly basic enough that a high concentration of peracid can be built up in the system to permit a reasonable rate of reaction with the electronically hindered olefin. Although the usual function of the base is to remove carboxylic acid preferentially to peracid, and hence to avoid hydroxylation, Na_2HPO_4 is not basic enough to remove all the trifluoroacetic acid formed. However, glycidic acid esters are sufficiently inert to epoxide opening by acids that a high carboxylic acid concentration can be tolerated. A stronger base such as sodium carbonate leads to low yields with unsaturated esters but to high yields with terminal olefins, which are ordinarily sluggish in their reactivity toward peracids. The weak base cannot be used to epoxidize ordinary olefins.

Olefin	% yield epoxide	Base	Notes
hexene-1	91	Na_2CO_3	
	40	Na_2HPO_4	+ 60% of hydroxy-trifluoroacetate.
cyclohexene	74	Na_2CO_3	
methyl methacrylate	84	Na_2HPO_4	
	13	Na_2CO_3	
ethyl methacrylate	81	Na_2HPO_4	
ethyl crotonate	73	"	
ethyl acrylate	54	"	
hexadiene -1,5	70	Na_2CO_3	diepoxide

DIENES

As suggested in the table above, a useful reagent to obtain diepoxides from unconjugated dienes is trifluoroperacetic acid-sodium carbonate. In general, conjugated dienes should react much more slowly than simple olefins to give monoepoxides. With perbenzoic acid in chloroform, oleic acid reacts (21) much faster than either linolenic acid, $CH_3(CH_2CH{=}CH)_3CH_2(CH_2)_6COOH$, or linoleic acid, $CH_3(CH_2)_4CH{=}CHCH_2CH{=}CH(CH_2)_7COOH$, which are not even conjugated olefins.

PHENYL CONJUGATION

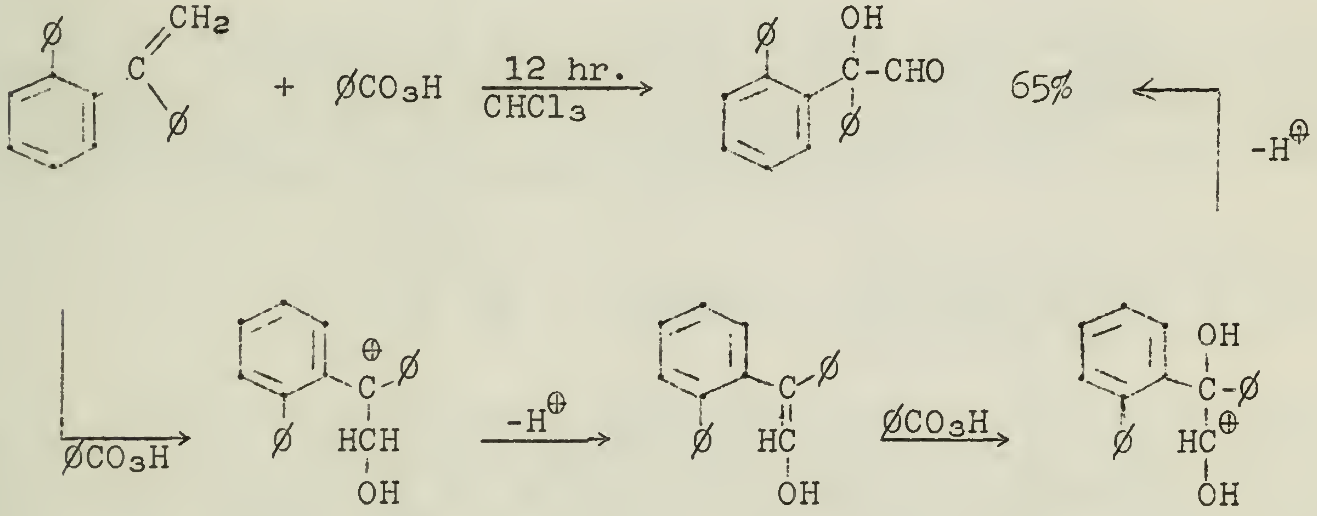
It was shown (22) qualitatively some time ago that conjugation of an olefin with a phenyl group increases its reactivity toward perbenzoic acid. Orders of reactivity are:

$$\text{Ø}CH{=}CHCH_3 \gg \text{Ø}CH_2CH{=}CH_2\text{, and}$$

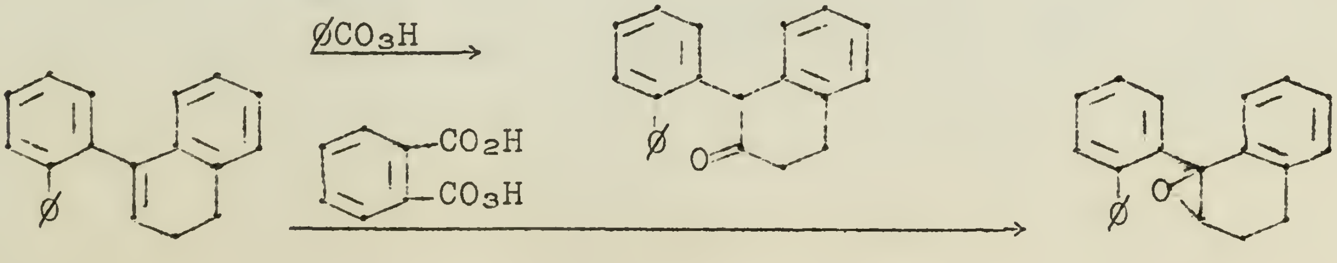
$$\text{Ø}CH{=}CHCH_2CH_3 \gg \text{Ø}CH_2CH{=}CHCH_3 > \text{Ø}CH_2CH_2CH{=}CH_2.$$

Cis- and trans-isomers were not indicated, and it is assumed that, where they exist, the trans-isomers were studied. In general, electron-withdrawing substituents on the benzene ring decrease the rate of epoxidation of the olefin.

Not always is the expected epoxide formed. Weisenborn and Taub (23) have found that the product of the reaction between 1-phenyl-1-(2-biphenylyl)-ethene and perbenzoic acid is phenyl-(2-biphenylyl)-hydroxyacetaldehyde, which might be formed through the intermediates (23) shown below.



Similiarly, a hindered olefin which, upon treatment with monoperphthalic acid (24) yielded the normal epoxide, upon treatment with the more active reagent, perbenzoic acid (23), gave rise to a ketone.

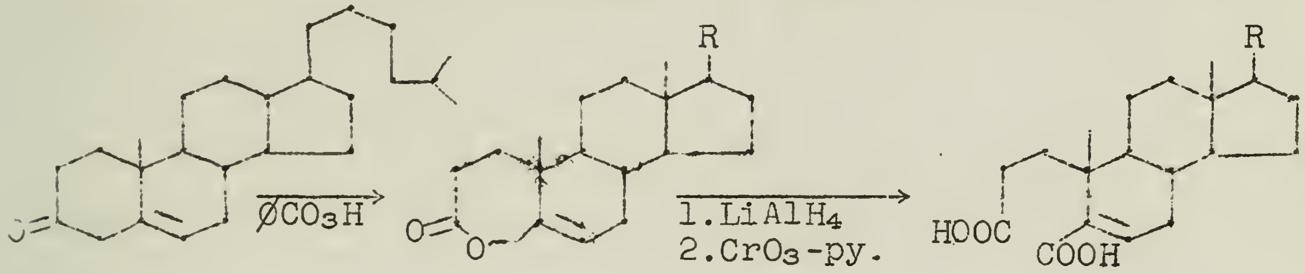


Curtin and Bradley (25) observed a similar type of reaction when 1-p-anisyl-1-phenylethene was treated with perbenzoic acid in chloroform. At -10° the expected epoxide was presumably formed, since from the bisulfite adduct was obtained the free p-anisylphenylacetaldehyde in 40% yield. However, at room temperature the product was found to be α-hydroxy-p-anisyl-phenylacetaldehyde (30-50%). This product probably was not formed through the enol form of the aldehyde, since the aldehyde obtained from the low temperature reaction, upon treatment with perbenzoic acid, was converted in 23% yield (based on isolated product) to p-methoxybenzhydrol.

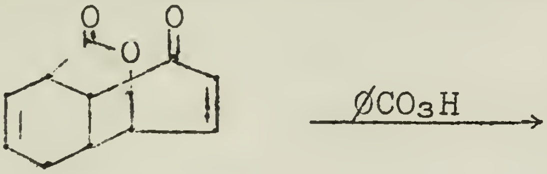
One might make a tentative generalization and suppose that in systems of the type Ø$_2$C=CHR there might be formed carbonyl products, specifically, Ø$_2$CHCOR or Ø$_2$C(OH)COR. Indeed, the simple system CH_2=CØ$_2$ gave rise to Ø$_2$CHCHO in 35% yield. (26)

TRANSANNULAR CONJUGATION. β,γ-Unsaturated ketones.

When Δ^5-cholestenone was treated with perbenzoic acid a lactone was formed (27) rather than the expected epoxide. Treatment of the product with lithium aluminum hydride gave a diol which showed no carbonyl absorption in the infrared and which yielded the known 3,4-seco-Δ-cholesten—3,4-dioic acid upon oxidation with CrO_3-pyridine.

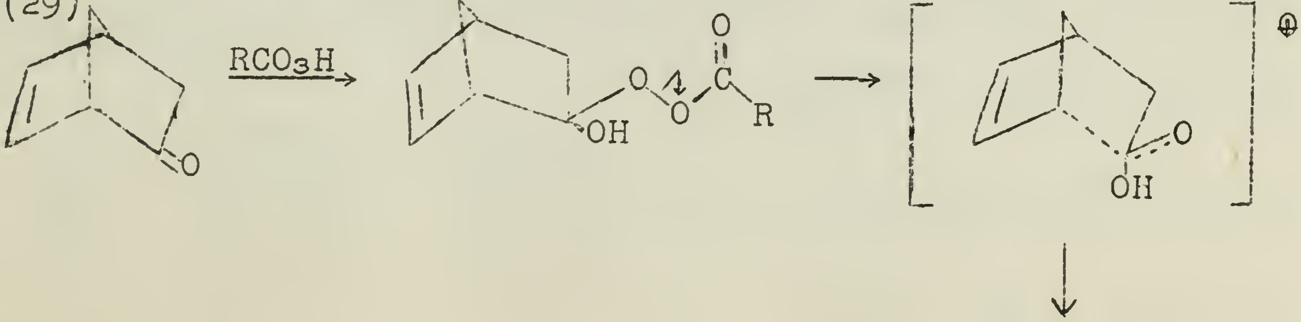


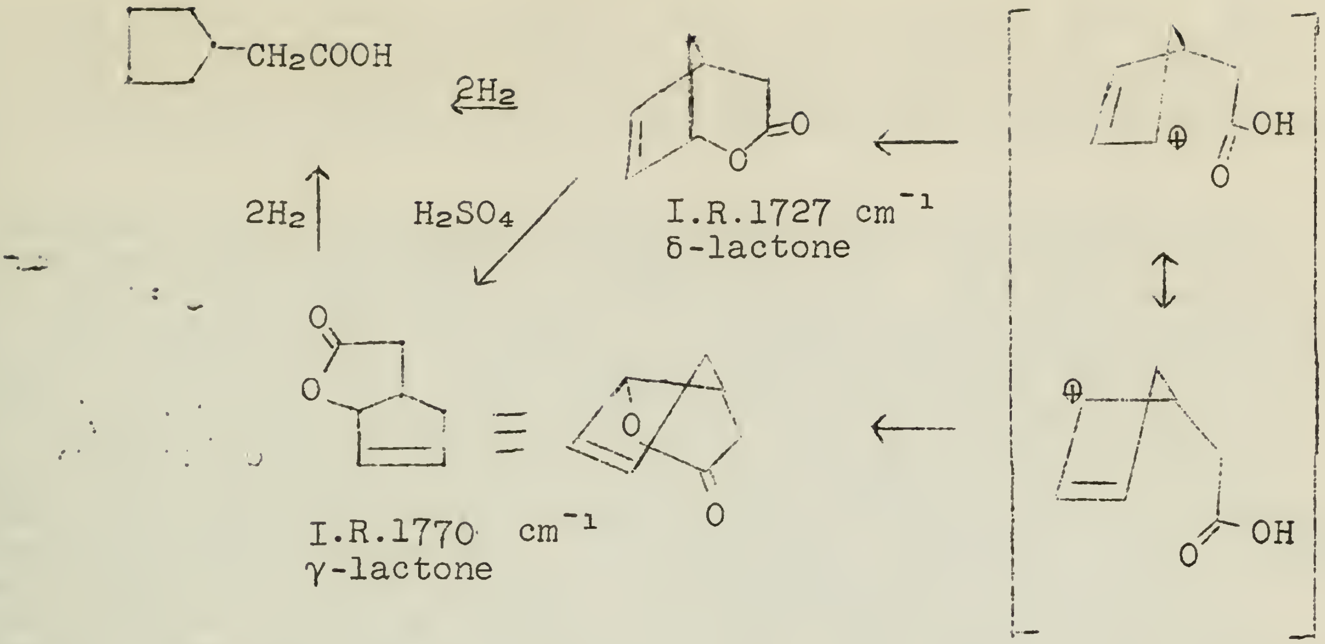
It is reasonable to believe that attack on the olefinic bond is hindered by transannular interactions of the ketone carbonyl with the double bond. A similar effect was noted by workers (28) who attempted to oxidize selectively the non-conjugated double bond in the following compound but found it electronically hindered.



continual slow uptake of
[0] past 1 mole to give
undefined products.

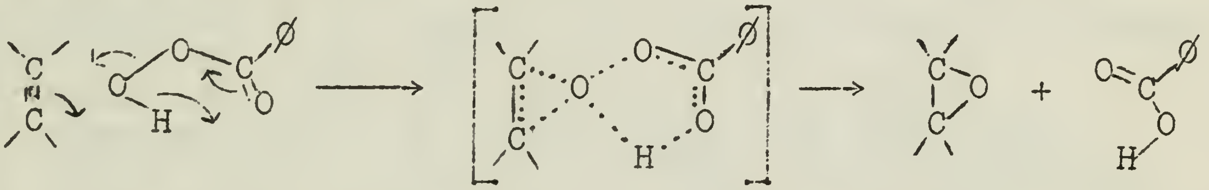
A careful study was made by Meinwald, Seidel, and Cadoff (29) of the reaction of dehydronorcamphor with peracetic acid under the conditions necessary (30) to convert norbornene to its epoxide. It was found that, rather than the epoxide, two lactones were formed which could be separated by chromatography and which gave the same product on hydrogenation. A possible mechanism for their formation was proposed (29).





MECHANISM OF PERBENZOIC ACID EPOXIDATION.

Swern (31) demonstrated in 1947 that, because olefinic reactivity is dependent upon electron-attracting or withdrawing properties of substituents, peracids are electrophilic reagents. One theory held that attack proceeded via HO$^+$ (23) produced by self-ionization of the acid. Other work has shown that HO$^+$ is not formed under the usual (non-ionic) conditions of the reaction. That the ionization of the peracid could not be a rate determining step was demonstrated by Lynch and Pausacker (32), who added magnesium perchlorate to the reaction mixture of cyclohexene and perbenzoic acid in ether and observed no change in the oxidation rate. It was later shown (33) by ^{18}O isotope tracer studies that no exchange between peracids and their corresponding anions takes place and that, therefore, free OH$^+$ are not present in the reaction mixture. In view of the added facts that only cis-addition (2) occurs and that perbenzoic acid appears from its infrared spectrum to be highly hydrogen bonded internally, Bartlett's original postulation (34) of a molecular, cyclic mechanism is currently accepted as the most reasonable.



Evidence has been compiled (32) to show the effect of altering the electronic atmosphere of the double bond in substituted stilbenes upon the rate of epoxidation with perbenzoic acid. The effects of p-substituents on the peracid are also evident from the data in the following summary of extremes gleaned from a longer list contained in the original source.

	Low	High
$\Delta H^{\ddagger}$	13.8 (a)	16.6 (b)
$\Delta F^{\ddagger}$	20.4 (c)	23.3 (b)
$-\Delta S^{\ddagger}$	21.1 (c)	23.1 (a)

(a) ØCH=CHØ + p-NO_2-$C_6H_4CO_3H$.
trans

(b) p-NO_2-C_6H_4-CH=CHØ + ØCO_3H.
trans

(c) p-MeOC_6H_4-CH=CH-C_6H_4OMe-p
trans
+ ØCO_3H.

These data showed a good correlation with σ^+ constants (35). The writer calculated ρ from the data and found it to be -1.2. This indicates that in the transition state a certain amount of positive charge is developed on the carbon atom alpha to the electron-donating group.

In some instances a glycol monobenzoate ester is the only product obtained from perbenzoic acid epoxidations. Campbell and coworkers (35) showed that there occurs an initial, non acid-catalyzed, second order epoxidation, followed by a slower ring-opening which is catalyzed by benzoic acid, when trans-p-methoxystilbene is treated with perbenzoic acid. Evidence in support of this contention is twofold. A plot of the formation of benzoic acid vs. time included a maximum with a steep ascent, indicating that after a point a slow reaction which destroys benzoic acid takes precedence over an initial fast reaction which produces it. In addition, the glycol ester formed in the presence of initially pure ^{14}C benzoic acid contained the activity expected from the statistically occurring reactions of epoxide with free ^{14}C and ^{12}C benzoic acid. This demonstrates the presence of a free intermediate, since no exchange between the nonlabeled ester with ^{14}C benzoic acid was observed.

It is interesting to note that trans-p-methoxystilbene yields the threo-glycol monobenzoate ester on treatment with perbenzoic acid and that cis-p-methoxystilbene yields the erythro-isomer (36), demonstrating that the ring is opened in the cis manner. Campbell (35) reported as a second product from this reaction phenyl p-methoxybenzyl ketone in 6% yield which increased to 18% when wet benzene was used as solvent.

****

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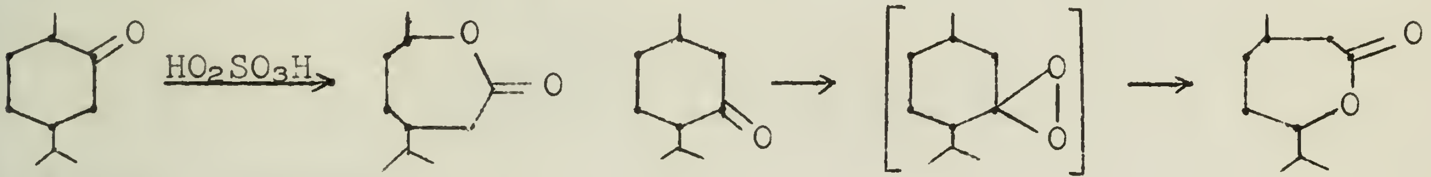
THE MECHANISM OF THE BAEYER-VILLIGER REACTION"

Reported by D. H. Gustafson April 23, 1959

INTRODUCTION

Organic peracids were discovered around the turn of the century and since then have been used extensively as oxidizing agents for organic compounds[1]. Peracids readily lend themselves to quantitative and kinetic studies, since the unconsumed peracid can be rapidly determined iodimetrically at suitable time intervals[1]. This seminar will present the work done on the mechanism of the oxidation of ketones to esters(Baeyer-Villiger reaction) by organic peracids. The other reactions of peracids and the synthetic aspects of this reaction have been reviewed elsewhere[1,2,3].

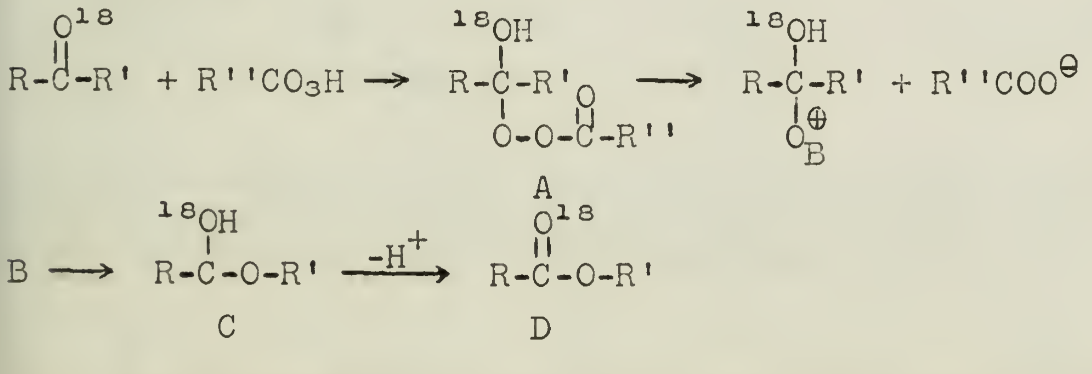
The oxidation of ketones to esters was first observed by Baeyer and Villiger[4] in 1899 when they treated menthone(IV), tetrahydrocarvone(I), and camphor with Caro's acid. At that time they proposed



I II IV III

that the simple oxooxide(III) was an intermediate in the oxidation of menthone(IV). This proposal has been shown to be incorrect by tracer experiments by Doering[5], who proved that the carbonyl oxygen of the ketone was the carbonyl oxygen of the ester and that no equilibration of oxygens had taken place.

In 1948 Criegee[6] proposed a mechanism that has now been generally accepted, although some of the details are still in doubt. It was assumed that the peracid first adds to the ketone yielding a hydroxyperoxide A (which has been called the Criegee intermediate). This intermediate then dissociates to give an electron deficient ion B which rearranges to C. Loss of a proton in the normal way then gives the ester D.



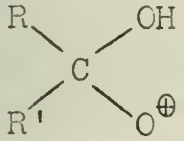
$$R-\overset{O^{18}}{\overset{\|}{C}}-R' + R''CO_3H \longrightarrow \underset{A}{R-\overset{^{18}OH}{\overset{|}{\underset{\underset{O-O-\overset{O}{\overset{\|}{C}}-R''}{|}}{C}}}-R'} \longrightarrow \underset{B}{R-\overset{^{18}OH}{\overset{|}{\underset{\underset{O}{|\oplus}}{C}}}-R'} + R''COO^{\ominus} \qquad (1)$$

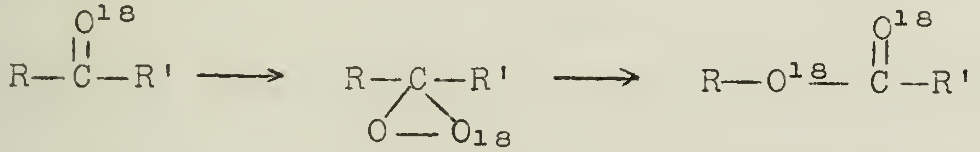
$$B \longrightarrow \underset{C}{R-\overset{^{18}OH}{\overset{|}{C}}-O-R'} \xrightarrow{-H^{+}} \underset{D}{R-\overset{O^{18}}{\overset{\|}{C}}-O-R'}$$

This mechanism is in accord with the observation that hydroxyhydroperoxides have been isolated and converted to esters by heating alone[8]. It explains the fact that the migratory aptitudes of aryl groups R or R' are normally proportional to their capacity for electron release[9]. One will note a general similarity of this mechanism with those established for the Beckmann, Curtius, Hofmann, pinacol-pinacolone, and acid-catalyzed hydroperoxide rearrangements[3].

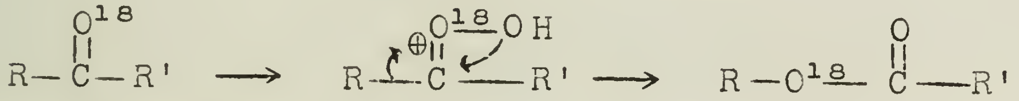
TRACER STUDIES

As mentioned above it was found[5], using oxygen labeled ketones, that the carbonyl oxygen of the ester came from the oxygen of the ketone. Burton, Lewis and Llewellyn[19] have also supported this finding with benzophenones and fluorenones. These results agree only with a mechanism of the Criegee type (eq. 1) and are completely incompatible with Baeyer's original proposal (eq. 2) or that proposed by Wittig[26] involving the additional of $OH^{\oplus}$ to the carbonyl oxygen of the ketone (eq. 3). It should be noted that if is an intermediate, it must be extremely short-lived or its oxygens would equilibrate through hydrogen transfer. The other possibility is that the rearrangement is concerted.





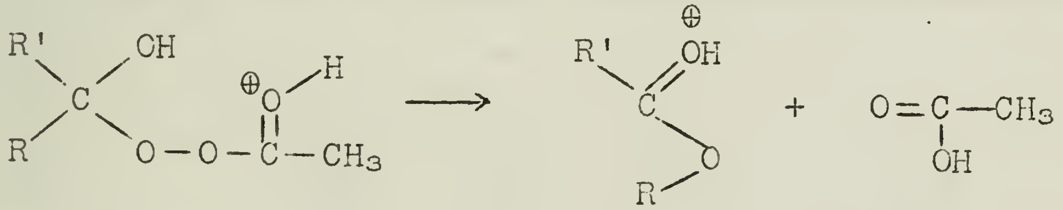
(2)



(3)

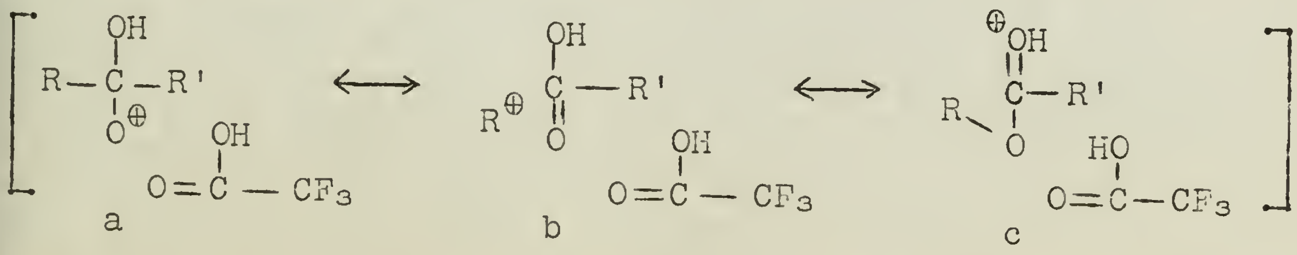
MIGRATORY ABILITIES

It has been established by Doering[9] that in the rearrangement step, the group which migrates is the one which can easier bear positive charge. The following order of migratory aptitudes for a series of substituted benzophenones was determined: *p*-anisyl and *p*-tolyl> phenyl> *p*-chlorophenyl, *p*-bromo-phenyl, *p*-nitrophenyl, and *p*-anilinium. The migratory aptitudes of alkyl groups follows the expected order tertiary> secondary> primary[10]. The rates of reaction approximated the migration aptitudes. These results can be explained by considering the reaction taking place as Criegee postulated except that the rearrangement of the alkyl or aryl group is concerted with the loss of carboxylic acid from the Criegee intermediate (eq. 4).



(4)

Structural effects in the migrating group which would lower the energy of a carbonium ion would be expected to increase the rate of rearrangement. Emmons and Lucas[11] have reasoned that resonance structures such as b must make a large contribution to the structure of the transition state for the rearrangement. The cleavage of the O—O bond is

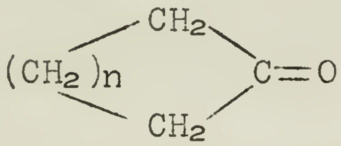


probably enhanced by the electronegative CF_3- substituent. It was also found[11] that methyl groups never migrate in methyl alkyl ketones, which is in agreement with this explanation.

A study of the effect of ring size of cyclic ketones on the rate found that a six-membered cyclic ketone is the most reactive[12]. These results can be explained in terms of relief of eclipsing strain. However, the low reactivity of cyclobutanone is somewhat surprising since a lesser degree of strain would be inherent in the transition state for a rate determining addition or coordination process than that present in the initial ketone. This should cause high reactivity. The relatively low Arrhenius activation energy and high $\Delta S^{\ddagger}$ for cyclobutanone (table I) indicates that there must be a steric inhibition of vibration or rotation resulting in low reactivity.

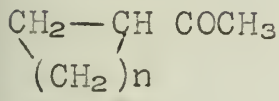
Table I

Thermodynamic Parameters for B-V Reaction of Cyclic Ketones of the Type



n	E^{Arr} (kcal/mole)	$\Delta F^{\ddagger}$ (kcal/mole)	ΔS (e.u.)
1	9.1	24	-54
2	15.4	22.1	-24
3	11.6	20.7	-33
4	13.3	24.0	-38
5	14.7	24.3	-34

Table II

Ketone  n	$k_2 \times 10^4$	rel. rate	E^{Arr} kcal/mole	$\Delta H^{\ddagger}$ kcal/mole	$\Delta F^{\ddagger}$ kcal/mole	$\Delta S^{\ddagger}$ e.u.
1	0.22	0.16	—	—	—	—
2	3.19	2.26	10.1	9.5	22.3	-43
3	1.13	0.80	11.5	10.9	22.7	-40
4	1.41	1.00	11.0	10.4	22.7	-41
5	1.14	0.81	10.5	9.9	22.8	-43
isopropyl	1.17	0.83	—	—	—	—

The results[12] of a study of the effect of ring size on the reaction rate of series of acetylcyclanes with perbenzoic acid are summarized in table II. If carbonyl addition of perbenzoic acid or of some ionic entity derived from it is the rate determining step, the rate will depend on both the electronic and the steric environment of that group. The thermodynamic quantities of activation indicate that any electronic effects are nearly constant throughout the series. Differences in the reactivity due to steric factors would be expected to show in differences in $\Delta S^{\ddagger}$; however since $\Delta S^{\ddagger}$ is relatively constant for this series, there must be no enhanced reactivity of any ketone

[illegible]

[illegible]

[illegible]

[illegible]

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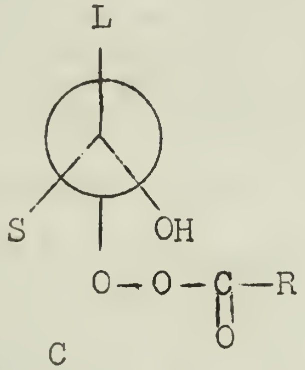
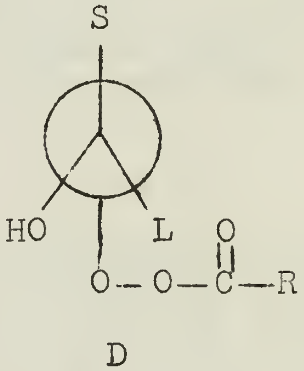
due to the steric environment of its carbonyl group. The cyclopropyl group has the most favorable geometry for addition to the carbonyl group, and therefore the reduction in the activity must be solely electronic.

Saunders[18] has shown that a group with a poor migratory ability can sterically hinder a group with a better migratory ability to such an extent that the poor group will rearrange preferentially over the better one. Such is the case with cyclohexyl phenyl ketone where the cyclohexyl group migrates five times as well as phenyl. Models show that cyclohexyl offers much interference to the preferred rotational conformation of phenyl for its migration. The conformation phenyl must take to migrate is such that the π-electrons of the ring may overlap the vacant (or partially vacant) p-orbital left by the leaving group at the migration terminus. Hawthorne[21] explains the rate differences observed in a competitive process such as t-butyl and phenyl vs. ethyl and phenyl (39 vs. 7×10^{-2}) might be the result of steric acceleration of migration of the more bulky alkyl group. If one assumes that the alkyl group which migrates enters the transition state trans to the leaving carboxylic acid group, then the sterically favored transition state would be that one which staggers the leaving group between the smaller alkyl group and the hydroxyl group. Migration of the larger alkyl group would then occur by way of the sterically preferred transition state C.



C

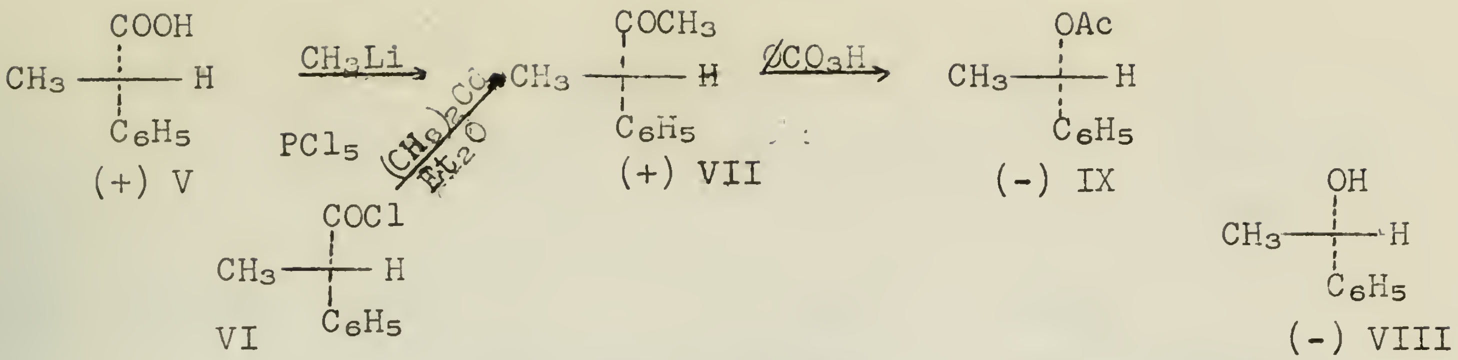


D

In comparing the effects of different peracids, it was observed[21] that a greater selectivity of cleavage is obtained when using peraceti acid than when using peroxytrifluoroacetic acid. The explanation for this is that migration must occur while the carboxylic acid residue is leaving the Criegee intermediate. More driving force is supplied by the migrating group when the leaving group is triflouroacetate than when it is acetate. This would be expected if the Criegee intermediate is a high energy complex which passes over an energy barrier in the ionization-rearrangement reaction, since the more reactive adduct with trifluoroperoxyacetic acid would undergo the least change in arriving at the transition state.

STEREOCHEMISTRY OF THE BAEYER-VILLIGER REACTION

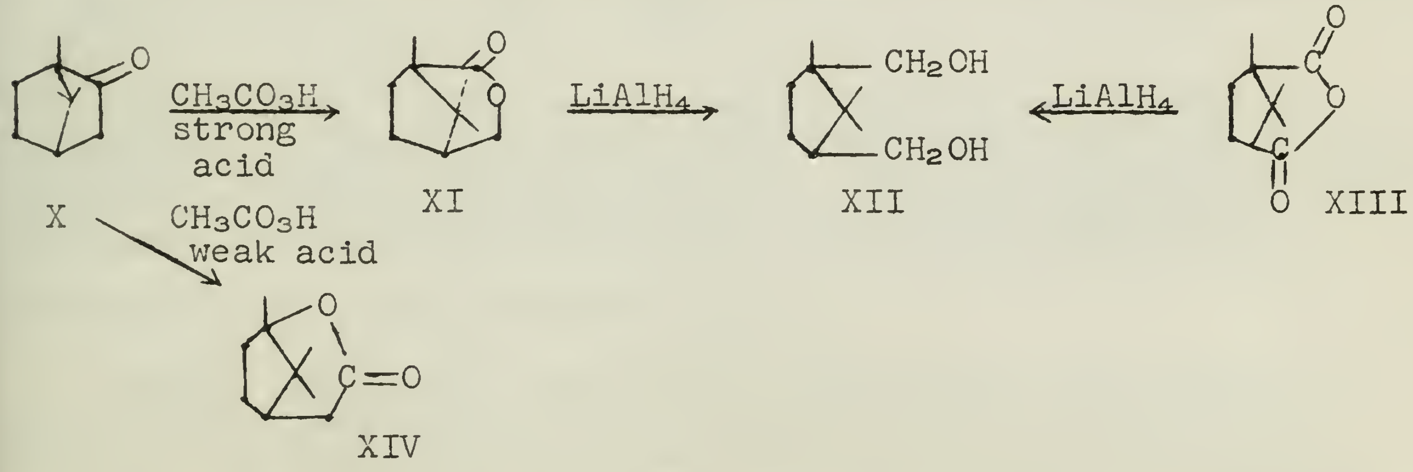
When 3-phenyl-2-butanone was treated with perbenzoic acid, the α-phenethyl group migrated with complete retention of its configuration[14]. The configuration of the phenylmethylcarbinylacetate was determined in the following way:



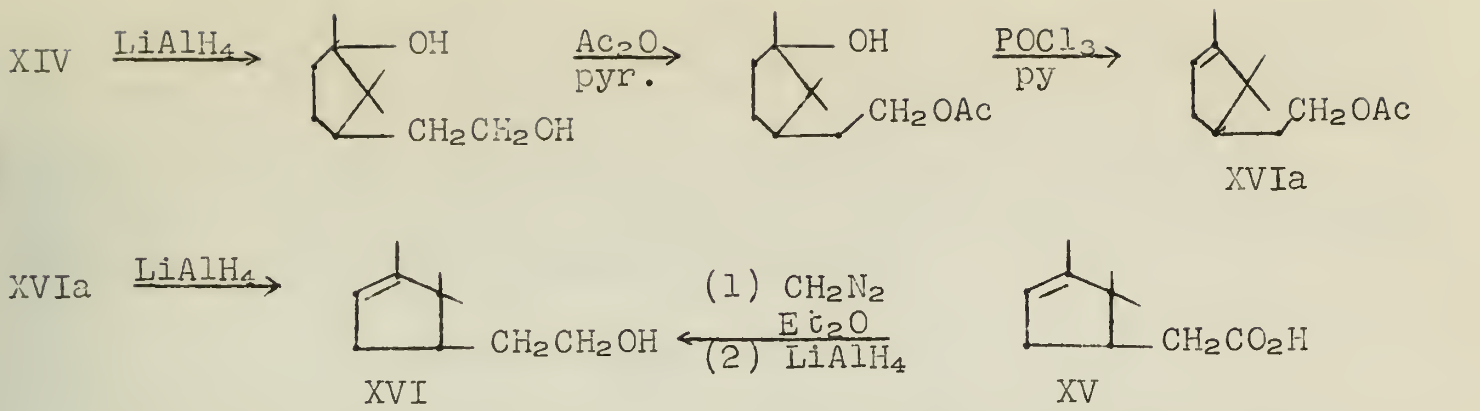
The configuration of (+) V is known and therefore (+) VII has the same configuration since it was prepared without affecting the asymmetric center. The configuration of (-)-phenylmethylcarbinol (VIII) is known and therefore that of its acetate (IX) is the same. Mislow[15] has confirmed that (+) V and (-) VIII are identically related to each other by relating both to mandelic acid; therefore, (+) VII and (-)-IX are related identically. The complete retention of asymmetry indicated a stereospecific reaction. The rearrangement of cis- and trans-2-methylcyclohexyl methyl ketone with perbenzoic acid proceeds with complete retention of configuration[16]. The cis- and trans-2-methylcyclohexylacetates were isolated sterically pure with no other products being formed. The cis- and trans-2-methylcyclopentyl methyl ketones yielded the same results. It has been found[17] that neopentyl methyl ketone and neophyl methyl ketone can be oxidized to the corresponding neopentylacetate and neophylacetate with complete retention of structure. The above results all tend to support the conclusion that the rearrangement step is concerted with the loss of carboxylic acid from the Criegee intermediate.

EFFECT OF STRONG ACID ON PRODUCT COMPOSITION

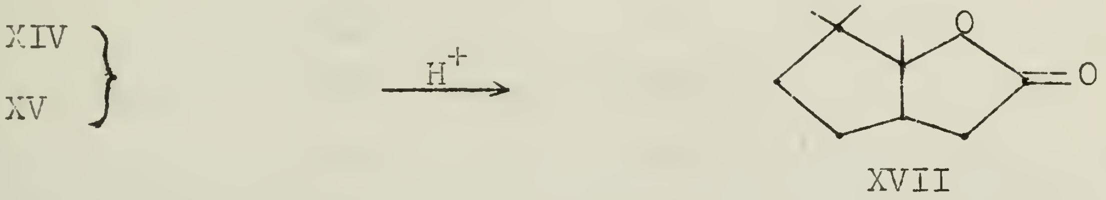
Sauers[20] has recently reinvestigated the oxidation of camphor (X) with peracetic acid. He has duplicated Baeyer's original findings[4] on treatment of camphor with peracetic acid in a solution of sulfuric acid and acetic acid 40:60. The lactone XI was converted to the known diol XII with lithium aluminum hydride. The diol XII was also prepared from the known anhydride XIII with lithium aluminum hydride.

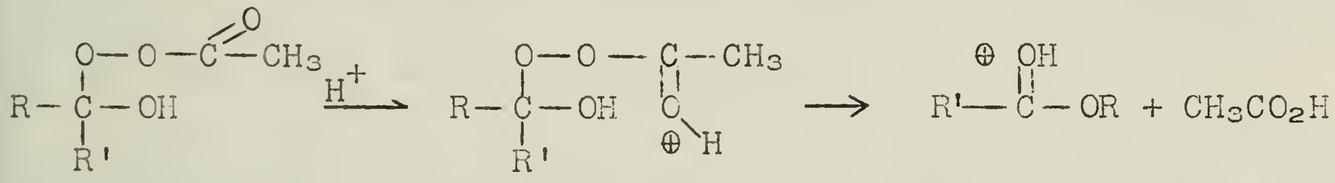


However, treatment of camphor with peracetic acid containing sodium acetate resulted in the formation of the isomeric lactone XIV. The tructure of XIV was proved in the following way:



The unsaturated alcohol XVI was identical with that prepared from α-campholenic acid XV. One will note that the lactone XIV can be derived from α-campholenic acid XV, and consequently it should be isomerized by acid to dihydro-β-campholenolactone XVII, which was accomplished in 87% yield. Treatment of α-campholenic acid resulted in the same product. It was thought that perhaps XIV was produced first in the reaction and then isomerized to XI since Baeyer[4] had reported finding another lactone but could not isolate it. However, treatment of either XIV or XVII with peracetic acid in the sulfuric acid-acetic acid solvent afforded no isomerization. Sauers accordingly postulated a modification of the Criegee mechanism under strong acid conditions. This modification is protonation of the Criegee intermediate, which would lower the activation energy of the rearrangement since now the leaving group would be neutral.





This lowering of the activation energy would probably result in a compression of the energy scale for rearrangement, allowing alternate reactions to compete more successfully. The transition state would be shifted toward the peroxyester with a concomitant deëmphasis of the importance of electronic stabilization of the migrating group.

KINETICS OF THE BAEYER-VILLIGER REACTION

Friess[7] studied the kinetics of the reaction of a series of substituted acetophenones with perbenzoic acid in chloroform, in 40:60-chloroform:*sym*-tetrachloroethane, and in 40:60-chloroform: methanol. He found that those ketones having electron withdrawing groups in either the *meta* or *para* position of the benzene ring obeyed the following first order rate law:

$-d(\text{peracid})/dt = k_1(\text{peracid})$, and that those ketones having electron donating groups in either the *meta* or *para* positions of the benzene ring obeyed the following second order rate law:

$$-d(\text{peracid})/dt = k_2(\text{peracid})(\text{ketone}).$$

Acetophenone exhibited a mixed order between one and two. Furthermore, he found acid catalysis and that the effect of substituents on the rate of reaction paralleled their ability to donate electrons to the carbonyl group of the ketone. It is interesting to note that the effect of the same substituents on semicarbazone formation is identical[13]. Increasing the polarity of the solvent also increased the rate of the reaction. In order to explain these results Friess postulated the following general mechanism:

$$\text{H}^{\oplus} + \text{peracid} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \begin{array}{c} \text{RCOOH} + \text{OH}^{\oplus} \\ \text{or} \\ \text{RCOOH} + \ddot{\text{O}}\colon \end{array}$$

$$\text{Ketone} + \text{OH}^{+} \;(\text{or } \ddot{\text{O}}\colon) \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} \text{Complex A}$$

$$\text{Ketone} + \text{peracid} \underset{k_{-3}}{\overset{k_3}{\rightleftharpoons}} \text{Complex B}$$

$$\text{Complex A} \xrightarrow{k_4} \text{product} + \text{H}^{+}$$

$$\text{Complex B} \xrightarrow{k_5} \text{product} + \text{RCO}_2\text{H}$$

From this mechanism, the following general rate law can be derived:

$$-d(\text{peracid})/dt = k_1(\text{peracid}) + k_3(\text{ketone})(\text{peracid})(k_5/k_{-3} + k_5) \quad (5)$$

Now, in equation (5), if $k_1 \gg k_3$ or $k_{-3} \gg k_5$ then (5) reduces to the first order equation observed for ketones having electron withdrawing substituents. However, if $k_1 \ll k_3$ and k_{-3} is small, then (5) reduces to the second order equation observed for ketones having electron donating substituents. For acetophenone neither of these extremes must hold, and the mixed mechanism predicted is observed. One important point has been overlooked which is this. The first order rate law predicts that all those ketones which obey it should do so at the same rate, which is not observed.

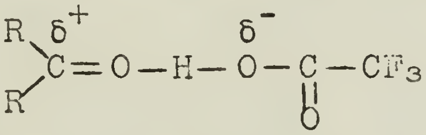
Hawthorne[22] has re-examined the kinetics of this reaction using peroxytrifluoroacetic acid and the same series of ketones. Contrary to the results of Friess[7], Hawthorne has found that in ethylene chloride the reaction is second order (first order in peracid and first order in acid catalyst), and in acetonitrile-ethylene chloride (10:1) the reaction is third order. In acetonitrile, the observed rates were found to fit the following rate expression:

$$-d(\text{CF}_3\text{CO}_3\text{H})/dt = k_3(\text{ketone})(\text{CF}_3\text{CO}_2\text{H})(\text{CF}_3\text{CO}_3\text{H}). \quad (7b)$$

After approximately 25% reaction, the pseudo first order plots of log $[\text{CF}_3\text{CO}_3\text{H}]$ vs time developed curvature showing autocatalysis. Under pseudo first order conditions (i.e. large excess of ketone and varying amounts of trifluoroacetic acid catalyst) in ethylene chloride, the pseudo first order rate constants were found to be independent of initial ketone concentration, but dependent on initial trifluoroacetic acid concentration. No evidence of autocatalysis during the first 50% of reaction was observed due to the fact that the trifluoroacetic acid produced was consumed by transesterification of the ester produced during the reaction. Furthermore, the pseudo

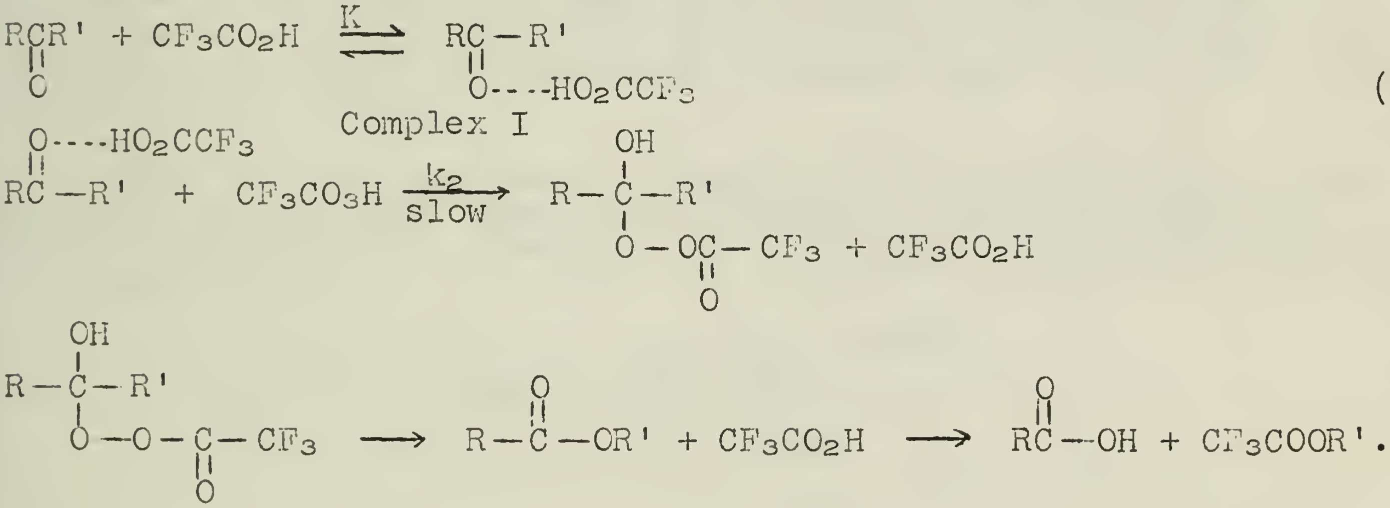
first order rate constant was dependent on the identity of the ketone, and therefore the rate determining step must involve this reactant. These results can be explained in terms of a transition state containing ketone, acid catalyst, and peracid if the ketone is completely complexed by one of the other reactants.

It was found that a considerable amount of heat was evolved when trifluoroacetic acid and the ketone were mixed in ethylene chloride. Moreover, the ultraviolet spectra of these solutions are quite different from those of the constituents separately. All the ketones studied showed a large hypsochromic shift and an increase in the extinction coefficient. These shifts are probably due to $N \rightarrow \pi$ transitions, a result supported by Nagakura *et al*[25]. Hawthorne postulated the complex to be



Further proof that such a complex exists is that *m*- and *p*-nitroacetophenone give approximately third order kinetics in ethylene chloride. The carbonyl oxygen of these ketones is too weakly basic for extensive formation of the hydrogen-bonded complex. In acetonitrile the complex must be completely dissociated.

An explanation for the change in order of the reaction with a change in solvent is as follows. Consider the following mechanism:



$$\mathrm{R\underset{\underset{O}{\|}}{C}R' + CF_3CO_2H \overset{K}{\rightleftharpoons} \underset{\text{Complex I}}{R\underset{\underset{O\text{----}HO_2CCF_3}{\|}}{C}-R'}} \qquad (6)$$

$$\mathrm{R\overset{\overset{O\text{----}HO_2CCF_3}{\|}}{C}-R' + CF_3CO_3H \xrightarrow[\text{slow}]{k_2} R-\overset{\overset{OH}{|}}{\underset{\underset{O-O\underset{\underset{O}{\|}}{C}-CF_3}{|}}{C}}-R' + CF_3CO_2H}$$

$$\mathrm{R-\overset{\overset{OH}{|}}{\underset{\underset{O-O-\underset{\underset{O}{\|}}{C}-CF_3}{|}}{C}}-R' \longrightarrow R-\overset{\overset{O}{\|}}{C}-OR' + CF_3CO_2H \longrightarrow R\overset{\overset{O}{\|}}{C}-OH + CF_3COOR'.}$$

The rate of the reaction will then be: rate $= k_2(CF_3CO_3H)$(complex I) and (complex I)$=K(RCOR')(CF_3CO_2H)$, where K is the equilibrium constant for equation (6). If A_t is defined as the stoichiometric amount of trifluoroacetic acid present (*i.e.*, $A_t =$ (complex I) + (CF_3CO_2H)) then the concentration of the complex is

$$(\text{complex I}) = \frac{K(RCOR')(A_t)}{1 + K(RCOR')}$$ and the rate expression

becomes
$$\text{rate} = \frac{k_2K(RCCR')A_t)(CF_3CO_3H)}{1 + K(RCOR')} \qquad (7)$$

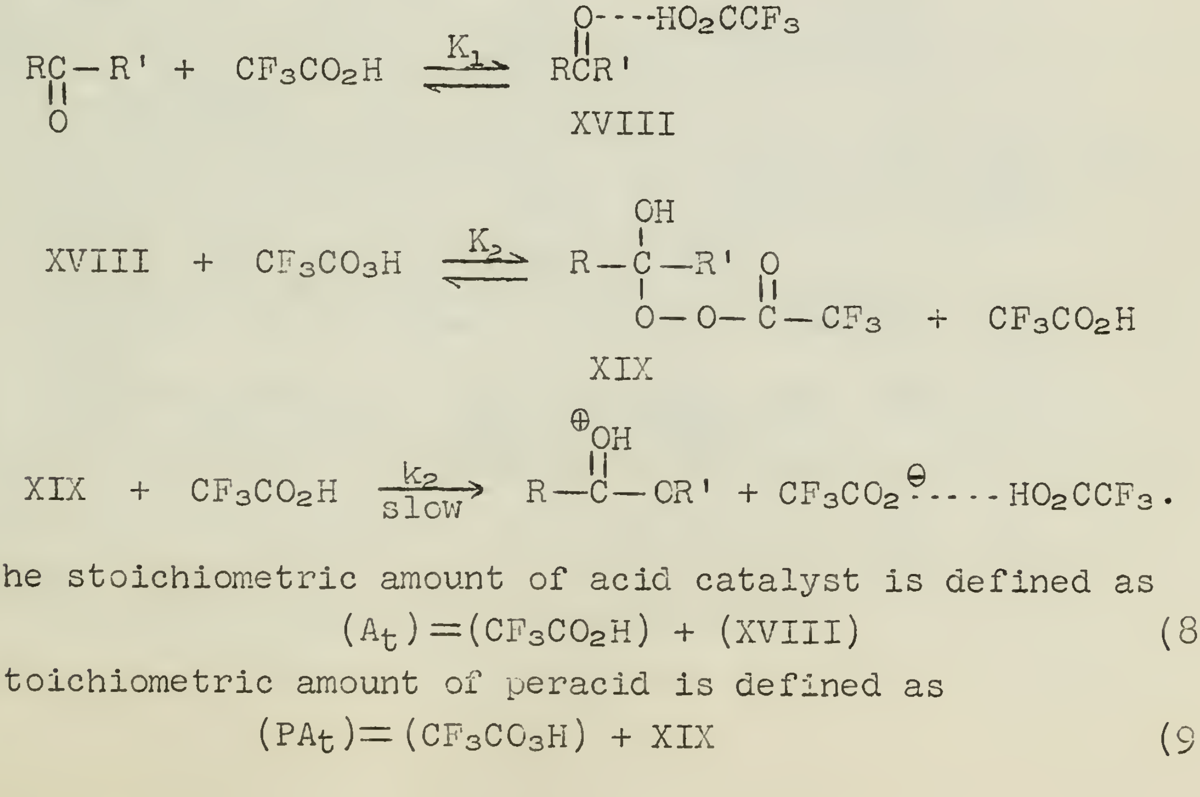
$$\text{rate} = k_2\ (\text{complex I})(CF_3CO_3H) \qquad (7a)$$

In ethylene chloride, K must be very large ($A_t \approx$ (complex I)) and consequently (7) reduces to the observed second order rate law (7a).

Conversely, in acetonitrile K must be very small $(A_t \approx CF_3CO_2H)$ and (7) reduces to the observed third order rate law (7b).

Hammett treatment of a series of substituted acetophenones gives linear σ plots in both ethylene chloride and 10:1 acetonitrile-ethylene chloride solvents, ρ being -1.10 and -1.45 respectively. For normal acid catalyzed carbonyl reaction, ρ has been found to be positive and moderate in size[23] instead of negative and moderately large as is the case obtained here. This result implies that the bond-breaking, acid-catalyzed, heterolysis of the Criegee intermediate is the rate controlling step. Fitzpatrick and Gettler[24] have shown that the rates of simple carbonyl addition reactions such as oxime and semicarbazone formation may be correlated by a simple linear free energy relationship. If the rate controlling step of the Baeyer-Villiger reaction were the slow addition of the peroxyacid to the protonated carbonyl group of the ketone, then one might expect a linear relationship to exist between the free energies of activation for the Baeyer-Villiger reaction and the free energy of activation for oximation of the same ketones. Hawthorne has stated that such a relationship does not exist; however close inspection of his data show that a rough correlation does exist for all the ketones studied except acetone, which reacts very slowly with peracid. This would lend support to Friess' conclusion that the rate determining step was the formation of the Criegee intermediate except for the case of acetone, but it fails to explain the large negative ρ. The sluggishness that acetone exhibits in the Baeyer-Villiger reaction may be explained by the fact that a very poor migrating group, methyl, must rearrange, and therefore the energy of activation is much higher in this case than in any of the others.

Since in the two cases previously mentioned[7,22], the solvents employed were not the same, a correlation of these two different results is difficult. However, the following mechanism accounts for the observations:



$$RC(=O)-R' + CF_3CO_2H \underset{}{\overset{K_1}{\rightleftharpoons}} RC(=O\cdots HO_2CCF_3)R' \quad \text{XVIII}$$

$$\text{XVIII} + CF_3CO_3H \overset{K_2}{\rightleftharpoons} R-C(OH)(R')-O-O-C(=O)-CF_3 \;(\text{XIX}) + CF_3CO_2H$$

$$\text{XIX} + CF_3CO_2H \xrightarrow[\text{slow}]{k_2} R-\overset{\oplus}{C}(=OH)-OR' + CF_3CO_2^{\ominus}\cdots HO_2CCF_3.$$

If the stoichiometric amount of acid catalyst is defined as

$$(A_t) = (CF_3CO_2H) + (\text{XVIII}) \qquad (8)$$

and the stoichiometric amount of peracid is defined as

$$(PA_t) = (CF_3CO_3H) + \text{XIX} \qquad (9)$$

and $\text{rate} = k_2K_1K_2(\text{RCOR}')(\text{CF}_3\text{CO}_2\text{H})(\text{CF}_3\text{CO}_3\text{H})$ (10)

then substitution of (8) and (9) in (10) gives (11)

$$\text{rate} = \frac{k_2K_1K_2(\text{RCOR}')(\text{PA}_t)(\text{A}_t)}{[1 + K_1(\text{RCOR}')][1 + K_1K_2(\text{RCOR}')]} \quad \text{or}$$

$$\text{rate} = \frac{k_2K_1K_2(\text{RCOR}')(\text{PA}_t)(\text{A}_t)}{1 + K_1(\text{RCOR}') + K_1K_2(\text{RCOR}') + K_1^2K_2(\text{RCOR}')^2} \qquad (11)$$

If K_1 or K_2 is large, the reaction becomes second order. The effect of the polar solvent would be to reduce K_1 and hence reduce XVIII, making the reaction third order. The effect of an electronegative substituent is to increase K_2 faster than it decreases K_1, making $K_1K_2(\text{RCOR}')$ large, and thus making the reaction second order.

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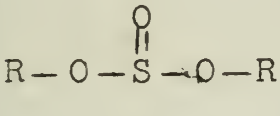
NUCLEOPHILIC DISPLACEMENTS IN ORGANIC SULFITES

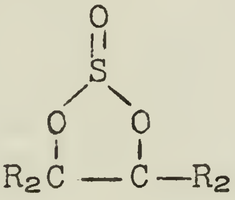
Reported by J. Witt April 27, 1959

This seminar deals with some simple displacements in which a nucleophilic agent reacts with the sulfite and replaces sulfur dioxide. The organic sulfites may be divided into two classes, the dialkyl or diaryl sulfites (A) and the cyclic sulfites which usually exist as the 1,2 (B) or the 1,3 (C) compounds.

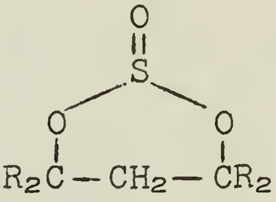


$R-O-\overset{O}{\overset{\|}{S}}-O-R$

(A)

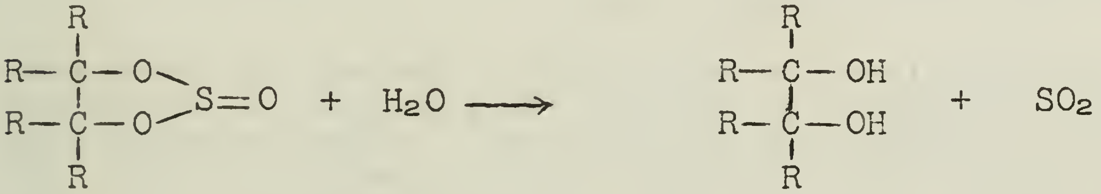


(B)



(C)

The overall nucleophilic displacement by water may be represented as follows.



POSITION OF BOND FISSION

A number of workers have investigated some nucleophilic displacements in sulfites to determine the position of bond fission, whether the carbon-oxygen or the sulfur-oxygen bond is broken during the course of the reaction.

de la Mare and his coworkers (1) prepared a series of cyclic sulfites which were hydrolyzed in both acidic and alkaline aqueous solutions. The position of bond fission was then determined by isotopic means. The hydrolysis was carried out in a solution of the sulfite and enriched water (H_2O^{18}). The resultant diol was recovered and pyrolyzed to carbon monoxide on red-hot carbon at low pressure in a radio frequency heater. The carbon monoxide was then analyzed mass-spectrometrically to determine whether any O^{18} was present in the diol. The results obtained are shown in Table I.

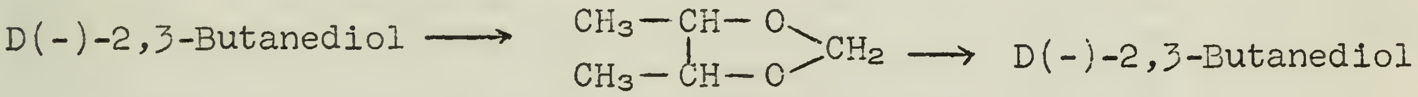
TABLE I

	O^{18}(atom % excess)*	
Sulfite	Alkaline hydrolysis Diol	Acid hydrolysis Diol
Ethylene	.005	.006
Propylene	.003	.000
meso-2,3-Butylene	.000	.033
Tetramethylethylene	.011	.024
Trimethylene	.022	.015
1,3-Butylene	.011	.025

* These values are relative to a sample of carbon monoxide obtained from the pyrolysis of oxalic acid.

The diol produced in all reactions studied, whether under acidic or alkaline conditions in enriched solvent, was isotopically normal. Therefore, sulfur-oxygen bond fission occurred in all these cases. Even under alkaline conditions with ethylene sulfite, structurally the most favorable for a bimolecular attack by hydroxide ion on carbon, and under acidic conditions with tetramethylethylene sulfite, structurally the most favorable for unimolecular carbon-oxygen heterolysis, the sulfur-oxygen bond was where fission occurred.

The optically active sulfite of 2,3-butanediol had been studied earlier by Garner and Lucas (2) to determine the location of bond fission during hydrolysis. This was done by carrying out the hydrolysis, converting the resulting diol to its formal for the purpose of removing it from a dilute aqueous solution, and comparing the optical properties of the formal with the properties of the active formal or with those of the *meso*-formal, the properties of which were known. The following process has been shown to occur without any change in rotation and configuration.



Therefore, the method of conversion to the formal and a study of its properties to determine any changes of configuration in the hydrolysis is valid. Hydrolysis of the sulfite of D(-)-2,3-butanediol yields a formal of high rotation, thus showing that the formation and hydrolysis of this sulfite does not involve any change in configuration, suggesting that the hydrolysis occurs with rupture of the sulfur-oxygen bond.

The cyclic sulfites of *cis*- and *trans*-cyclohexane-1,2-diol were hydrolyzed under acidic and alkaline conditions and the configuration of the diol obtained was determined by Foster, Hancock, and Overend (3). Table II summarizes the results.

TABLE II

Cyclic Sulfite	Conditions	Products
trans-Cyclohexane-1,2-diol	acidic	*trans*-diol
trans-Cyclohexane-1,2-diol	alkaline	*trans*-diol
cis-Cyclohexane-1,2-diol	acidic	*cis*-diol
cis-Cyclohexane-1,2-diol	alkaline	*trans*-diol and a small amount of *cis*-diol.

From these results it is seen that the hydrolysis occurs with a fission of the sulfur-oxygen bond with the exception of the *cis*-isomer under alkaline conditions. It was concluded that some carbon-oxygen bond fission occurred under the latter conditions.

Lieberman and coworkers (4) carried out a number of reactions with the sulfites of 3α-cholestanol and 3β-cholestanol. With aqueous acid, dry hydrogen chloride in methanol, or silver acetate in acetic acid, retention of configuration in the products indicated that these compounds react by a rupture of the sulfur-oxygen bond.

This cannot be accounted for by a double inversion as the sulfites were prepared by methods which do not involve the carbon-oxygen bond.

In the acid catalyzed hydrolysis, it may be postulated that a proton adds to an oxygen atom. This positive charge then weakens the sulfur-oxygen bond since a formal charge of plus two exists on the sulfur. The sulfur-oxygen bond is then cleaved by an attack of a solvent molecule on the sulfur, thus yielding the alcohol with the original configuration.

The formation of a carbonium ion is unlikely. There is the possibility that the carbonium ion could be so oriented that the entering group would attack the ion from one side preferentially. If this were the case, both the α- and β-isomers would give the same carbonium ion and subsequently yield the same isomer or mixture of isomeric alcohols. Since each sulfite was hydrolyzed with complete retention of configuration, the existence of a carbonium ion is unlikely. This concept is strengthened by the results of the dry hydrogen chloride-methanol reaction. Had this reaction taken place by a carbonium ion mechanism, the product would have been the methyl ether, which was not isolated. These results eliminate both the carbonium ion mechanism and a displacement reaction involving a cleavage of the carbon-oxygen bond.

In the reaction with silver acetate in acetic acid the uninverted alcohol was isolated along with an amount of cholestanol acetate. The cholestanol acetate produced was probably not produced by the displacement of $RSO_3^{\ominus}$ by acetate ion. Such displacement would lead to inversion and since this was not observed, the acetate must result from the secondary acetylation of the alcohol produced by the hydrolysis. In order to confirm this, it was found that cholestanol 3α-acetate was formed from 3α-cholestanol under the same experimental conditions used for the cleavage whereas cholestanol 3α-acetate was recovered unchanged. Some cleavage of the carbon-oxygen bond occurred as evidenced by the formation of a small amount of neocholestene.

The group at University College, London, has carried out an extensive study on the acid and alkaline hydrolysis of cyclic sulfites (1,5,6,7). The remainder of this seminar will deal with their work.

ACID HYDROLYSIS

Many acid catalyzed reactions fall into one of two classes, according to whether the rate of reaction is proportional to the stoichiometric concentration of acid or to the acidity as measured by Hammett's acidity function. A discussion of Hammett's acidity function, Ho, and its application in determining reaction mechanisms has been well reviewed (8,9).

The acid hydrolysis of ethylene sulfite was studied to determine whether it was dependent upon Ho or the molar concentration of acid. The reaction was carried out in perchloric acid and was followed well into the region of acidity in which Ho and the molar concentration are markedly different. The results are shown in Figure 1 and Table III.

Figure 1

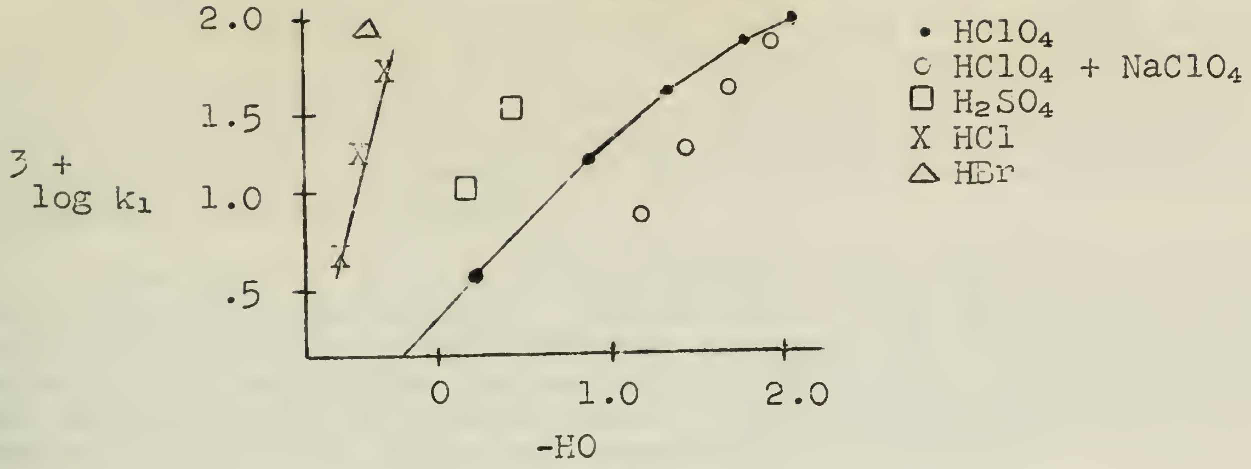


Table III

Ethylene sulfite at 44.6°

(conc. in mole liter^{-1}, k_1 in min^{-1}).

$HClO_4$	0.030	0.150	0.500	1.500	2.184	4.373
$10^4 k_1$	1.35	6.89	25.9	83.5	141*	476
$10^3 k_1/H^\oplus$	4.50	4.55	5.18	5.56	6.46	8.80
Ho	1.52	0.82	0.31	-0.44	-0.72	-1.74

* In 90% D_2O, $10^4 k_1$=213 min^{-1}.

If we consider only the effects of variation in the acid concentration, the values lie near a straight line of slope 0.68, though the graph shows an appreciable curvature at the higher acidities. For a reaction dependent upon Ho, a straight line of nearly unit slope would be expected.

A further criterion was investigated to determine if the reaction was dependent on Ho, this was the influence of added salts. If sodium perchlorate is added and the molar concentration of acid kept constant, the acidity of the solution as measured by Ho is increased considerably. However, the rates of these acid catalyzed hydrolyses are not increased. A combination of the above results seems to provide satisfactory evidence that the reaction is not dependent upon Ho.

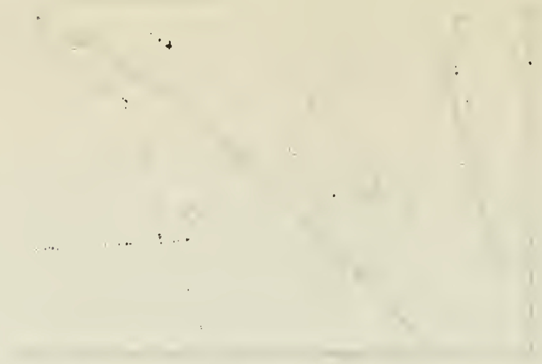
But the reaction is not concentration-dependent in the conventional sense. From the data in Table III, it is seen that the values of $k_1/H^\oplus$ vary. If the reaction is carried out under conditions in which the ionic strength is kept constant by the addition of sodium perchlorate, the rate is very nearly proportional to the concentration of perchloric acid. These facts along with the independence of Hammett's Ho suggest that the reaction is essentially concentration-dependent with a superposed dependence on the concentration of the added salt. Table IV summarizes these results.

Table IV

Ethylene sulfite at 44.6°

(conc. in mole liter^{-1}, k_1 in min.$^{-1}$)

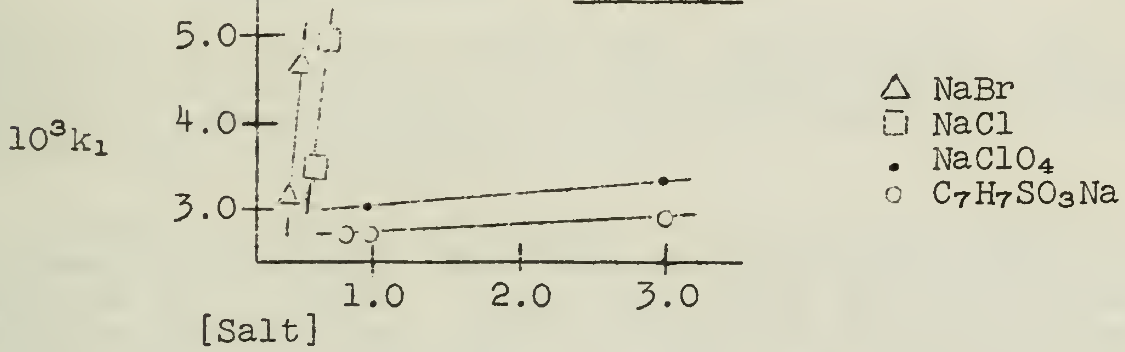
$HClO_4$	0.500	1.000	2.000	3.000
$NaClO_4$	5.500	5.000	4.000	3.000
$10^4 k_1$	78.6	185	397	610
$10^3 k_1/H^\oplus$	15.7	18.5	19.3	20.3
Ho	-1.00	-1.31	-1.73	-2.00



The hydrolysis has also been studied in acids other than perchloric. It might be expected that the rate of reaction would be affected in a specific manner by different electrolytes and this was verified experimentally. Figure 1 shows the effect of sulfuric, hydrochloric and hydrobromic acids in comparison with perchloric acid. At the same molar concentration of acid the four acids have widely different catalytic powers.

Catalysis of the reaction by added electrolyte is not limited to the region of high acidity. Salts have a very pronounced effect and fall into two fairly well-defined classes, the first, in which the effects are large, and the second, in which the effects are small. The reaction rate is proportional to the concentration of the salt. The effects of the salts are summarized in Figure 2.

Figure 2



With the results for perchloric acid being taken as the standard, it is seen that at high concentration of acids, the points representing catalysis by these acids lie markedly above the plot representing the relationship between Ho and the logarithm of rate. Even more, these acids have a greater catalytic power than expected from their molar concentrations. The effects of the negative ions fall in the order $Br^{\ominus} > Cl^{\ominus} > HSO_4^{\ominus} > ClO_4^{\ominus}$, which is the order of decreasing nucleophilic power. It seems reasonable therefore to attribute this type of catalysis to nucleophilic attack by the negative ion on the protonated sulfite.

The use of this information in determining the reaction mechanism can be seen on consideration of the Zucker-Hammett hypothesis (10). For an acid catalyzed reaction of a neutral molecule to give a transition state which involves only an added proton, the rate will increase in proportion to the Ho acidity function. However, if the reaction involves in addition a water molecule in the transition state, the rate will vary proportionally to the molar concentration of acid. The chief justification for the use of the hypothesis is the experimental one that it appears to fit a variety of reactions whose mechanisms are fairly well established by other criteria (9,11,12,13). The fact that the hydrolysis of the sulfite is not dependent upon Hammett's Ho is an indication that the reaction involves a water molecule in the transition state. This is further substantiated by the entropies of activation for the reactions.

The entropy of activation for the acid hydrolysis of ethylene sulfite was calculated to be -15.8 e.μ., the value for trimethylene sulfite was -13.0 e.μ.. The results are for hydrolyses in 1M perchloric acid.

The mechanism involving a molecule of water in the transition

state, called the A-2 class, should have a more negative entropy of activation than the mechanism which does not have a water molecule, called the A-1 class. This is because the A-2 type involves a relative increase of constraint on the reaction system due to orientation and reaction of a water molecule from the solvent. The entropies of activation for the acid hydrolyses of some compounds for which the mechanism has been established by other means are given in Table V (15).

Table V

Compound	Mechanism	ΔS^* (e.μ.)
Ethyl orthoformate	A-1	+5.8
t-Butyl mesitoate	A-1	+9
γ-Valerolactone	A-2	-24.6
Ethyl acetate	A-2	-23.0

Comparison of the above values with those obtained with the sulfites indicate a solvent molecule is involved in the transition state. This is in agreement with the conclusion reached on consideration of the rate and its independence of Ho.

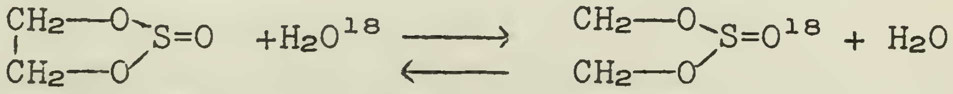
Ethylene sulfite was hydrolyzed at both high and low acidities in 90% heavy water (D_2O). The rate in D_2O is faster than in H_2O by a factor of 1.5 or more. It has been found that most acid-catalyzed reactions proceed more rapidly in D_2O than in H_2O if they undergo specific acid catalysis (14) which may be illustrated as follows.

$$S + H^{\oplus} \rightleftarrows SH^{\oplus} \qquad S=\text{substrate}$$

$$SH^{\oplus} \longrightarrow \text{products}$$

D_2O is less basic than H_2O and because of this, the substrate will be able to compete more effectively with the solvent for the proton in D_2O than in H_2O. Since the concentration of the conjugate acid of the substrate will be higher in D_2O, the rate of the reaction should be higher in D_2O than in H_2O, provided the second step does not show an isotope effect. General acid catalysis has a mechanism in which a proton is transferred from the acid to the substrate and from the substrate to a base in the rate-controlling step. In this case one would expect to obtain a normal isotope effect.

Isotopic exchange between the oxygen atom of the -S=O group and solvent is a possible process which would have an important effect upon the mechanism. Experiments were performed to determine whether this exchange occurred or not (1).



The sulfites were treated in enriched water with sufficient acid or alkali to react with half of the sulfite, the reaction was carried out, and the unreacted sulfite recovered and analyzed. Results are shown in Table VI.

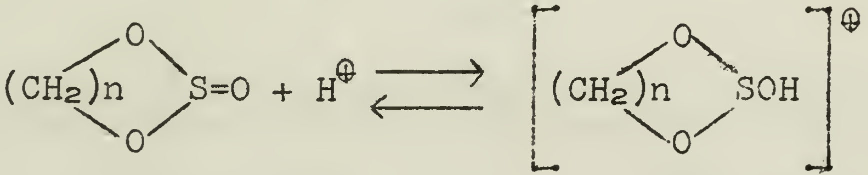
Table VI

		O^{18} (atom % excess)
Sulfite	Conditions	Sulfite (recovered)
Ethylene	alkaline	.016
"	acidic	.016
"	initially neutral	-.004
Trimethylene	alkaline	-.002

These results show that the exchange reaction does not occur in significant competition with the hydrolysis, either under acidic or alkaline conditions.

Mechanism for Acid Hydrolysis

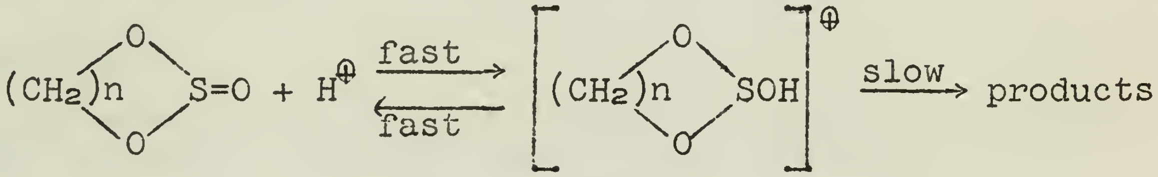
With the experimental evidence noted it is now possible to formulate a probable mechanism for the acid hydrolysis. The rate difference in deuterated water is characteristic of reactions which proceed by a pre-equilibrium proton-transfer which is probably the following.



(I)

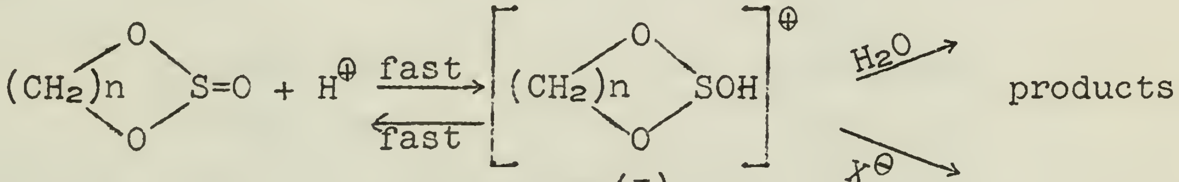
There is no evidence as to the exact position of the proton.

The evidence presented indicates that the displacement of sulfur dioxide is not a unimolecular reaction of the A-1 class. So the following type of mechanism is eliminated.



(I)

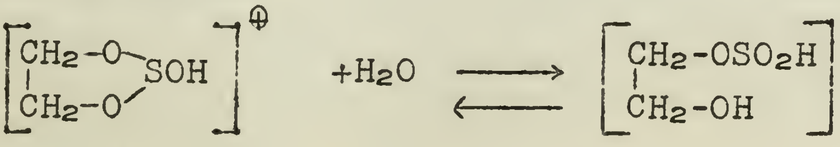
It seems probable that some nucleophilic agent is concerned in the rate-determining covalency change.



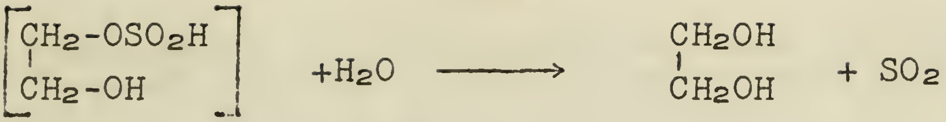
(I)

This type of mechanism would take into account the strong catalytic power of the added nucleophilic agents such as bromide and chloride.

If we consider the case where a molecule of water is acting as a nucleophilic agent and attacks the protonated sulfite, it may be postulated as follows.



(II) (III)

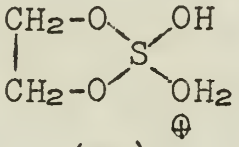


$$\left[\begin{matrix}CH_2\text{-}OSO_2H\\ CH_2\text{-}OH\end{matrix}\right] + H_2O \longrightarrow \begin{matrix}CH_2OH\\ CH_2OH\end{matrix} + SO_2$$

(III)

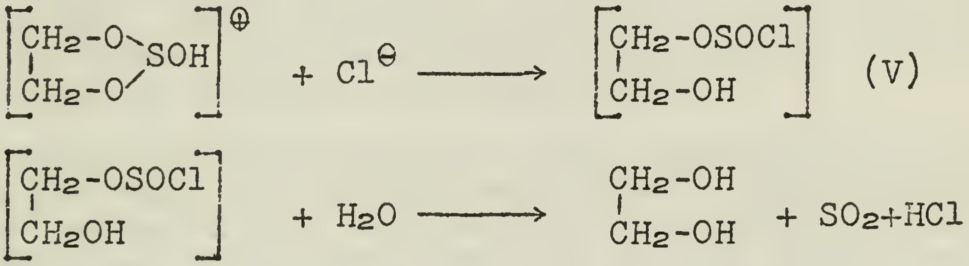
If the formation of an intermediate such as (III) were reversible to any appreciable extent, the oxygen of the water would equilibrate with the oxygen attached to the sulfur atom. It has been shown that this is not the case. Therefore, the intermediate (III) must decompose to products more rapidly than it reverts to reactants.

An alternative formulation of this intermediate is as in structure (IV), in which a water molecule has added to the S-O group. No distinction can be made between the possible intermediates but the same arguments exclude (IV) from being in reversible equilibrium with the reactants.



(IV)

If we consider the reactions where water is replaced by some other nucleophilic agent, the probable reaction scheme would be the following.

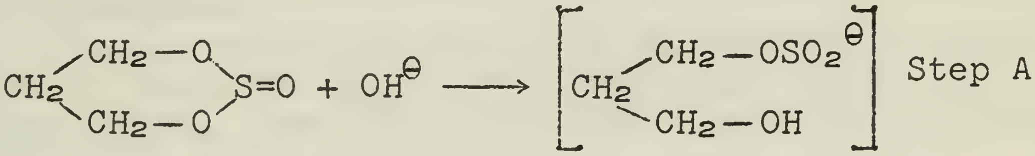


$$\left[\begin{matrix}CH_2\text{-}O\\ CH_2\text{-}O\end{matrix}\!\!>SOH\right]^{\oplus} + Cl^{\ominus} \longrightarrow \left[\begin{matrix}CH_2\text{-}OSOCl\\ CH_2\text{-}OH\end{matrix}\right] \quad (V)$$

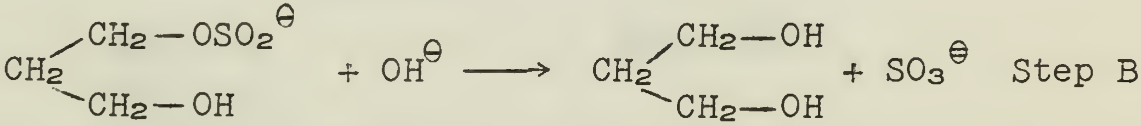
$$\left[\begin{matrix}CH_2\text{-}OSOCl\\ CH_2OH\end{matrix}\right] + H_2O \longrightarrow \begin{matrix}CH_2\text{-}OH\\ CH_2\text{-}OH\end{matrix} + SO_2 + HCl$$

Alkaline Hydrolysis

The alkaline hydrolyses of cyclic sulfites are more rapid than those in acidic solution. Possible steps in the reaction are as follows.



(VI)



Both steps have been shown to involve sulfur-oxygen bond fission. In principle either may be reversible and either may be rate determining.

Intermediate (VI) at the stage of half hydrolysis would be converted to its most stable prototropic form by rapid proton transfer. It is the anion of an acid of the type, $ROSO_2H$, which would be expected to be similar in strength to sulfurous acid in its first dissociation ($K_,=1.7x10^{-2}$). The sulfurous acid produced in the second stage is moderately strong in its first dissociation but weak in its second ($K_2=10^{-7}$). So any building-up of the intermediate (VI) could be measured by following the consumption of alkali by two indicators, to one of which sulfurous acid behaves as a monobasic acid and to the other as a dibasic acid.

Alkaline hydrolyses of the 1,2-sulfites were too rapid for convenient kinetic measurements, but it is assumed that the same considerations apply to these as to the 1,3-sulfites. The latter are hydrolyzed according to the kinetic form,

$$\frac{d(SO_2)}{dt} = k_2[\text{sulfite}][OH^{\ominus}],$$

the assumption being made that for every mole of $SO_3^{\ominus}$ formed, two moles of hydroxide were used up. The decrease in concentration of alkali, whether followed by titration to methyl red or to phenolphthalein obeyed the same rate law and proceeded at the same rate as the increase in concentration of sulfur dioxide which was determined by titration with iodine.

If step A was more rapid than step B and irreversible, intermediate alkylsulfonate ion (VI) would build up in concentration during the reaction. If the intermediate did not react with iodine, as sulfur dioxide does, the rate of alkali consumption could not equal the rate of liberation of material that can be titiated with iodine. If, alternatively, the intermediate reacted with iodine, then different rates of disappearance of alkali would be observed, depending on which indicator was used for the titration. However, it was found that the disappearance of alkali based on titration with either indicator and the liberation of material titratable with iodine have the same rates. Therefore, the second step of the reaction must be much more rapid than the first, and the intermediate does not build up in concentration during the course of the reaction.

Another possible reaction scheme is that the intermediate is in equilibrium with the reactants. This would give a rapid equilibration between the oxygen atoms of the $-SO_2$ which are structurally equivalent in the ion. It has been shown that there is no such equilibration. Therefore, the second step must be faster than the possible reverse step of stage A and the intermediate (VI) decomposes as rapidly as it is formed.

Effect of Structure on Rate

The effect of substituents in both acid and alkaline hydrolysis is small as might be expected since the substituent groups are removed from the reaction center. The relative rates of some acid hydrolyses are given in Table VII (1,5).

Table VII

Sulfite	Rel. Rate
Ethylene	1
*Propylene	1
(-)-2,3-Butylene	0.8
meso-2,3-Butylene	1.2
Tetramethylethylene	0.7
*1,3-Butylene	2.4
Trimethylene	4
*3-Chloropropylene	0.3

* - run at 100°, others run at 35°.

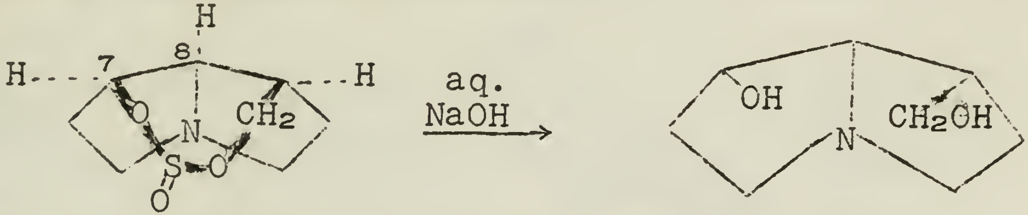
Changes in ring size have little effect on rate in acid hydrolysis which is in contrast to the situation in alkaline hydrolysis. The greater reactivity towards hydroxide of the 1,2- than the 1,3- cyclic sulfites is qualitatively similar to the behavior of the analogous

phosphates (16). This greater reactivity of the 1,2- sulfites may be due to strains in the five-membered ring, or to internal repulsions between the lone-pair elections of the oxygen atoms.

Acid hydrolysis of a dialkyl sulfite, dietlyl sulfite, is faster than either 1,2- or 1,3- cyclic sulfites (17). Alkaline hydrolysis of 1,3-cyclic sulfite is similar to that for dialkyl compounds, and both are much less reactive than the 1,2- cyclic compounds.

Applications to Other Systems

The conclusive findings of de la Mare and his group have application in stereochemical assignments in other systems. Thus, platynecine sulfite (VII), a *Senecio* alkaloid derivative, is hydrolyzed with aqueous sodium hydroxide to platynecine and since this is the precursor of the sulfite (18), the configuration of platynecine (VIII) at C-7 must be unchanged throughout.



(VII) (VIII)

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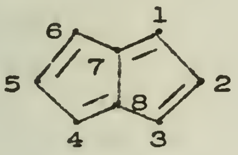
PENTALENES

Reported by R. K. Kurz April 30, 1959

INTRODUCTION:

Pentalene or bicyclo(3.3.0)octatetraene (I) is a member of the class of compounds which are termed the non-benzenoid aromatics or pseudo-aromatics. As a member of the non-benzenoid aromatics, pentalene and two of its derivatives, benzopentalene (II) and 1,2,4,5-dibenzopentalene (III) have been the subjects of much interest to both theoretical and synthetic organic chemistry. Of these three compounds, only 1,2,4,5-dibenzopentalene has been synthesized. The results of some of the theoretical treatments of these compounds and some of the synthetic investigations carried out in attempting to synthesize them are discussed in this report. Two reviews on pentalenes are available (1,2).



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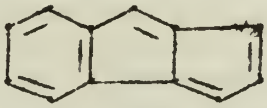

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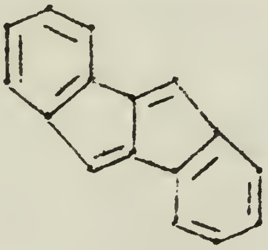

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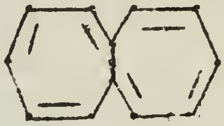

IV

THEORETICAL:

In 1922 Armit and Robinson (3) proposed pentalene as a possible aromatic hydrocarbon. Two resonance forms can be drawn for pentalene, and these indicate that pentalene should have a significant resonance stabilization energy. On the other hand, if the pentalene structure is viewed in the light of the concept of the aromatic sextet, it is evident that the 8π electron system of pentalene does not obey the $4n+2$ rule. formulated by Hückel (4), which characterizes the benzenoid aromatics. Pentalene, however, may be placed in the series of hydrocarbons formulated as containing $4n$ π electrons, of which cyclobutadiene, pentalene, and heptalene (IV) are the first three members.

The hydrocarbon azulene, which lacks the characteristic six-carbon cyclic structure of the benzenoids, does possess the requisite $4n+2$ π-electron system and a definite aromatic stability. This stability is believed to arise from the ability of both rings to maintain aromatic sextets through contributions of polar resonance structures in which the five membered ring attains the cyclopentadienyl carbanion structure, and the seven membered ring simultaneously attains the cycloheptatrienylium cation structure, both of which are known to be stable. However, each ring in pentalene possesses only five π electrons (5).

Quantum-mechanical calculations have been carried out on pentalene by a number of workers using the valence bond (VB) (6,7) and the molecular orbital (MO) approaches (7,8,9,10). More recently a third "non-empirical calculation" in which the special forms of the wave functions and the use of empirical parameters derived from benzenoid hydrocarbons were avoided has also been applied to pentalene (11). Benzopentalene and the two isomers of dibenzopentalene have been treated only by the MO method (12).

For pentalene both the VB and the MO methods predict high

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resonance stabilization energies of ca. 40 kcal./mole, but the two methods differ in their descriptions of the ground state of the molecule. The wave function in the VB method describing the most stable state of the electrons is antisymmetric, while in the MO method the ground state is described as totally symmetric. Because the MO treatment also predicts a non-homogenous distribution of the π electrons in pentalene (a result which occurs only with the non-benzenoid aromatics and is in contradiction to the initial assumption implicit in the method that the π electrons are uniformly distributed), the MO prediction has been held open to question, and the VB method was believed to give a more reliable definition of the ground state of pentalene The calculation of bond orders by the VB method results in the prediction of a small negative bond order of -0.056 for the 7-8 bond in pentalene. This reflects a repulsive force by the π electrons across this bond.

The lack of agreement between the results of the VB and MO calculations on pentalene as well as on the other pseudo-aromatics caused Craig to subject these systems to the third, "non-empirical method" (11). As a result of these calculations the pseudo-aromatics were predicted to have alternate long and short bond lengths, and resonance stabilization energies significantly lower than those predicted by the VB and MO methods. Furthermore, when the bicyclic structures of the pseudo-aromatics were compared to the corresponding monocyclic structures (e.g. pentalene to cyclooctatetraene), it was found that the resonance stabilization predicted for the bicyclic compounds was less than that for the monocyclic compounds (13). Thus pentalene has been predicted to possess the characteristics of a polyolefin and not those of an aromatic hydrocarbon. This characterization of pentalene as a reactive polyolefin is more in accord with the repeated failures to prepare the pentalene system intact, and with the observed chemistry of 1,2,4,5-dibenzopentalene.

The MO resonance energies for benzopentalene, 1,2,4,5-and 1,2,5,6-dibenzopentalene have been calculated to be 80, 120 and 110 kcal./mole, respectively (12). Just as in the case of pentalene, the MO treatment predicted a non-homogenous distribution of π electrons in these systems.

A comparison of the predicted diamagnetic anisotropy of the pentalene system (which can be obtained from the MO method) with that predicted for benzenoid aromatic systems reveals that, in the pentalenes, a decrease in the diamagnetic susceptibility should be observed as one proceeds from a direction in the plane of the molecule to the direction perpendicular to that plane. An increase in diamagnetic susceptibility during the same operation is predicted for benzenoid aromatics. Measurements of the diamagnetic anisotropy of 1,2,4,5-dibenzo-3,6-dimethylpentalene have substantiated the predicted decrease for the pentalene system (12).

SYNTHETIC:

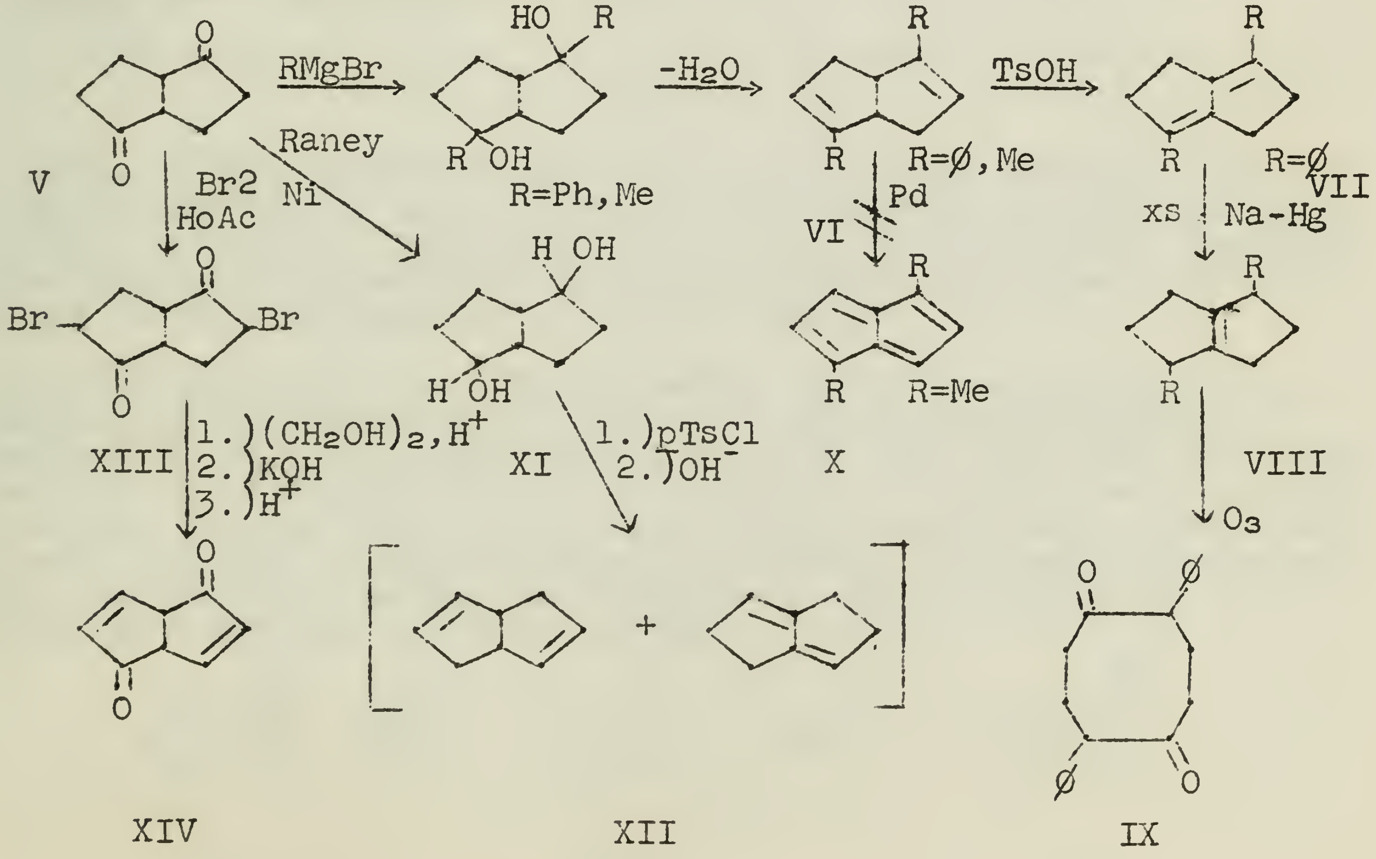
Most of the attempts to prepare pentalene or its substituted derivatives proceed from bicyclo(3.3.0)octane and its derivatives. The reactions discussed here are those illustrating the methods employed in achieving varying degrees and sites of unsaturation in bicyclo(3.3.0)octanes.

Dehydrogenation experiments on bicyclo(3.3.0)octane in the vapor phase over platinum, under conditions which converted decalin to

naphthalene, were unsuccessful (14). Liquid-phase dehydrogenation of 3-benzylidenebicyclo(3.3.0)octane using selenium catalyst resulted in partial decomposition of the starting material. 3-Bicyclo(3.3.0)octanol was recovered unchanged when similarly treated.

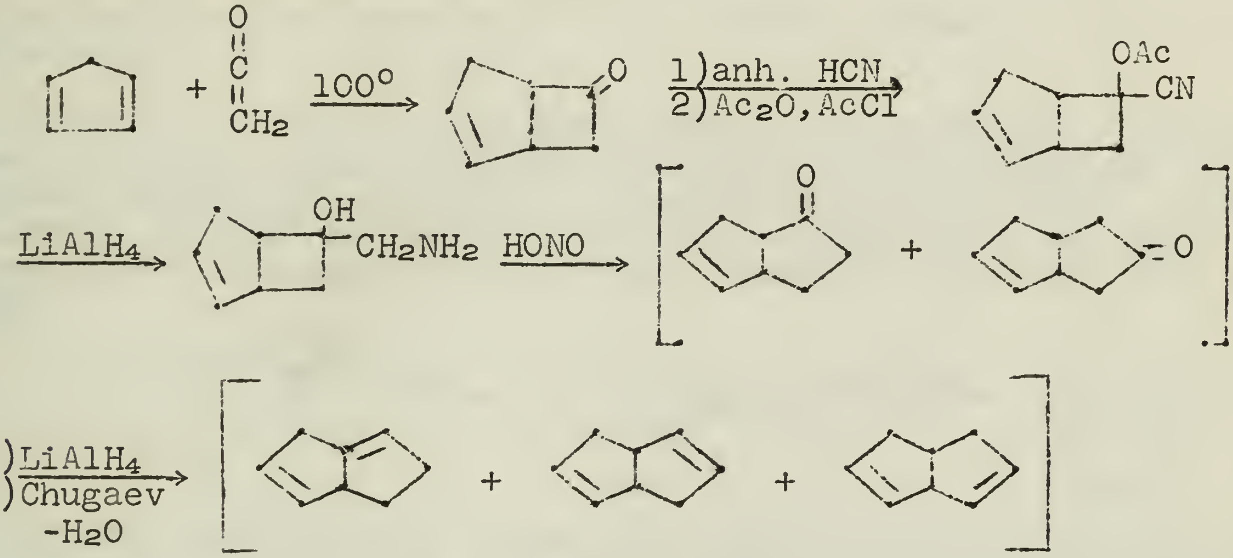
The diketone V, which is synthesized by means of the double Dieckmann condensation of 1,3,4,6-tetracarbomethoxyhexane followed by acid hydrolysis and decarboxylation of the condensation product (15) has been employed to prepare several tetrahydropentalenes. Reaction of this ketone with benzaldehyde in base led to the formation of 3,7-dibenzylidenebicyclo(3.3.0)octa-2,6-dione which showed no tendency to isomerize into a dibenzyldihydroxypentalene (15,16). Grignard reagents reacted with the diketone V to form tertiary alcohols which were dehydrated with $KHSO_4$, 50% oxalic acid or formic acid to yield tetrahydropentalenes of the type VI (16,17). 3,6,7,8-Tetrahydro-1,4-diphenylpentalene (VI, R= Ph) was rearranged by treatment with p-toluenesulfonic acid to the conjugated diene VII. An excess of sodium amalgam reduced this diene to the olefin VIII. Ozonolysis and reductive cleavage of the ozonide of VIII yielded the cyclooctadione (IX) (17). Catalytic dehydrogenation and disproportionation experiments on the dimethyl derivative of VI (R= Me) failed to convert it to 1,4-dimethylpentalene (X).

Reduction of V with Raney nickel or lithium aluminum hydride led to a mixture of bicyclo(3.3.0)octan-2,6-diol isomers (XI), which when treated with p-toluenesulfonyl chloride formed di-p-toluenesulfonates. Reaction of these sulfonates with aqueous alkali yielded a steam-volatile oil which was a mixture of tetrahydropentalenes (XII). The crude tetrahydropentalenes were treated with N-bromosuccinimide to form tetrahydrodibromopentalenes which were converted to the diethylamino derivatives. Hofmann degradation of the quaternized amines gave only a dark tarry residue (16).



Bromination of V in acetic acid led to the dibromide XIII (16,18). Diketalization of XIII followed by dehydrobromination of the diketal with KOH in ethanol and final acid hydrolysis of the diketal yielded the unsaturated ketone XIV (18). Treatment of the dibromide XIII with silver acetate yielded a ketonic, unsaturated material, possibly XIV, in very poor yield (16). The dibromide XIII failed to lose hydrogen bromide in boiling xylene, while thermal decomposition at 145° caused the evolution of hydrogen bromide and the formation of an unsaturated product which polymerized immediately. Dilute alkali or triethylamine liberated bromide ion and led to polymeric products that failed to give semicarbazones. N-Bromosuccinimide reacted readily with V, but the reaction product lost hydrogen bromide spontaneously, leaving a dark tar (16).

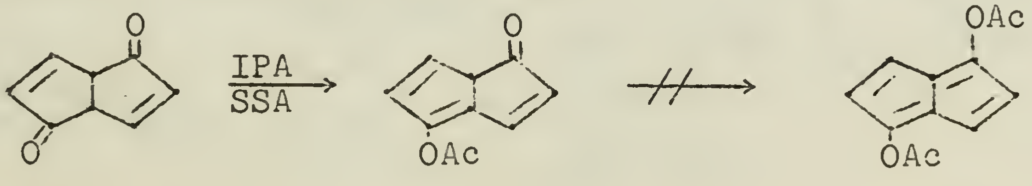
A mixture of tetrahydropentalenes in which the two double bonds were situated one in each ring of the bicyclo(3.3.0)octane skeleton, and were not conjugated, was synthesized from cyclopentadiene and ketene in the following manner (19):



XV

The mixture of dienes XV was reduced over palladium-charcoal catalyst with the uptake of two mole equivalents of hydrogen to give pure *cis*-bicyclo(3.3.0)octane. Dehydrogenation of XV over palladized charcoal or asbestos and halogenation-dehydrohalogenation experiments to form pentalene or dihydropentalene were unsuccessful.

Dauben, Juang and Ben (20) attempted forced enolization of 1,4-diketotetrahydropentalene (XIV) to obtain the pentalene system. Isopropenyl acetate and acetic anhydride with acid and basic catalysts led only to the decomposition of the diketone. In later work on this enolization, Osborne (18), using isopropenyl acetate with sulfosalicylic acid catalyst, likewise failed to obtain 1,4-diacetoxypentalene (XVII), but believed he may have prepared a small quantity of 1,7-dihydro-4-acetoxy-1-ketopentalene (XVI).



XIV XVI XVII

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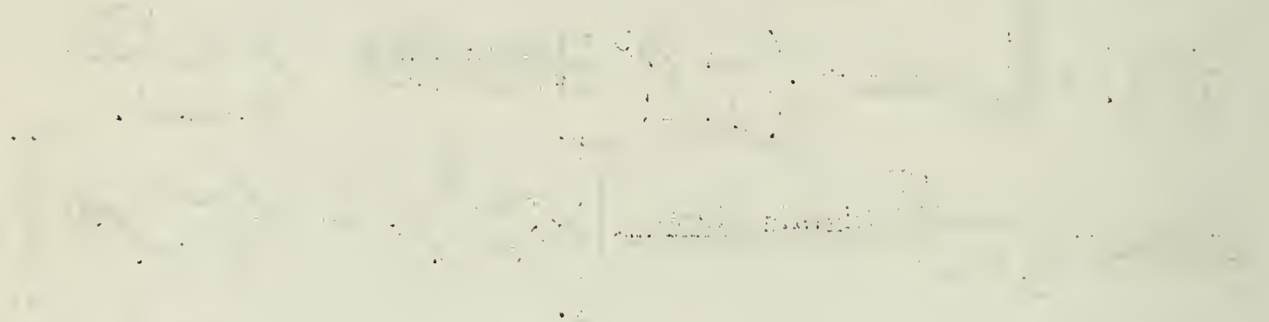

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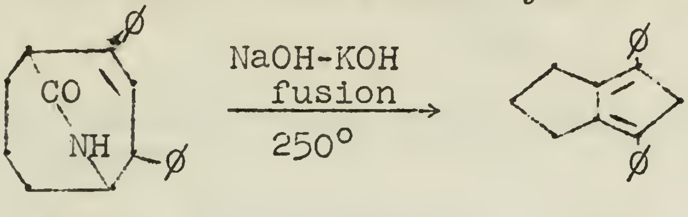
Mesitylmagnesium bromide formed an orange precipitate with XIV, which upon treatment with acetyl chloride resulted in the formation of a white, highly saturated, non-acetylated polymer. Titration of the diketone in ether with sodium triphenylmethylide led to brown precipitate, which on acidification with acetic acid at -70° formed a white polymer (20).

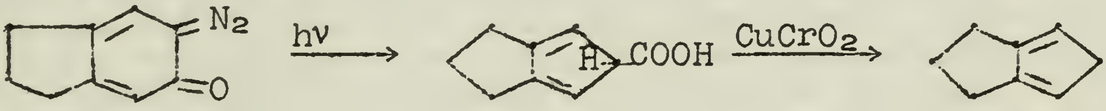
1,3-Diphenyltetrahydropentalene (XIX) has been obtained through fusion of the cyclooctene XVIII with alkali hydroxides at 250° (21).



XVIII XIX

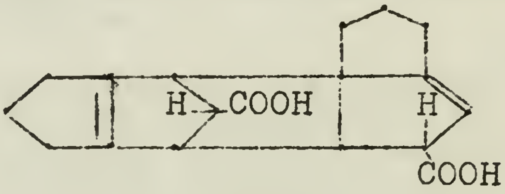
The structure of XIX was established through its UV spectrum (λ_{max} 242,359mμ), by catalytic hydrogenation to 2,4-diphenylbicyclo-(3.3.0)octane, and by ozonolysis which yielded glutaric acid and dibenzoylmethane.

As part of a study on the photochemical preparation of new ring systems, Süs et al. (22) prepared 2,4,5,6-tetrahydropentalene (XXII) from ortho-quinodiazidine (XX) by irradiation with UV light. The intermediate 2,4,5,6-tetrahydropentalene-2-carboxylic acid (XXI) was decarboxylated in quinoline with copper chromite under an inert atmosphere.



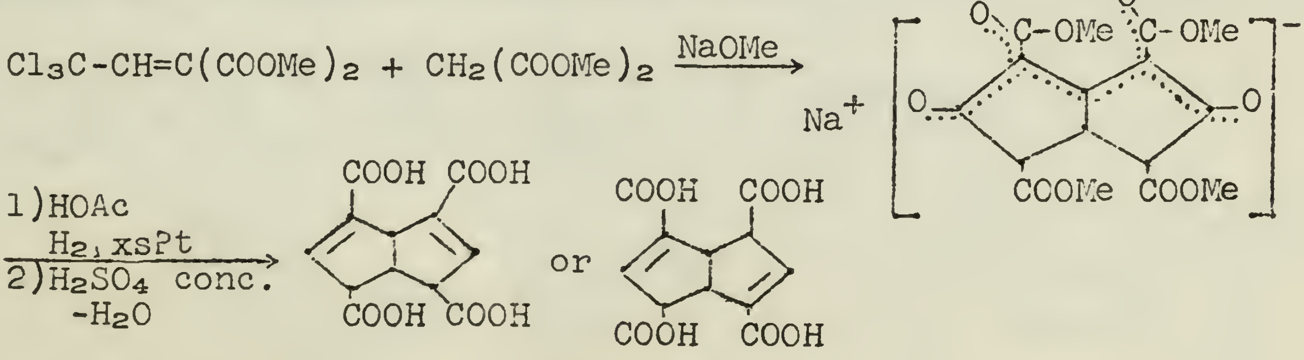
XX XXI XXII

In the presence of air, the diene XXII polymerized to a viscous red oil. A dimeric dicarboxylic acid of the type XXIII was also obtained during the isolation of the mono acid XXI. The formation of this dimer can be regarded to proceed by a Diels-Alder reaction with one molecule of XXI acting as the dienophile and a second acting as the diene.



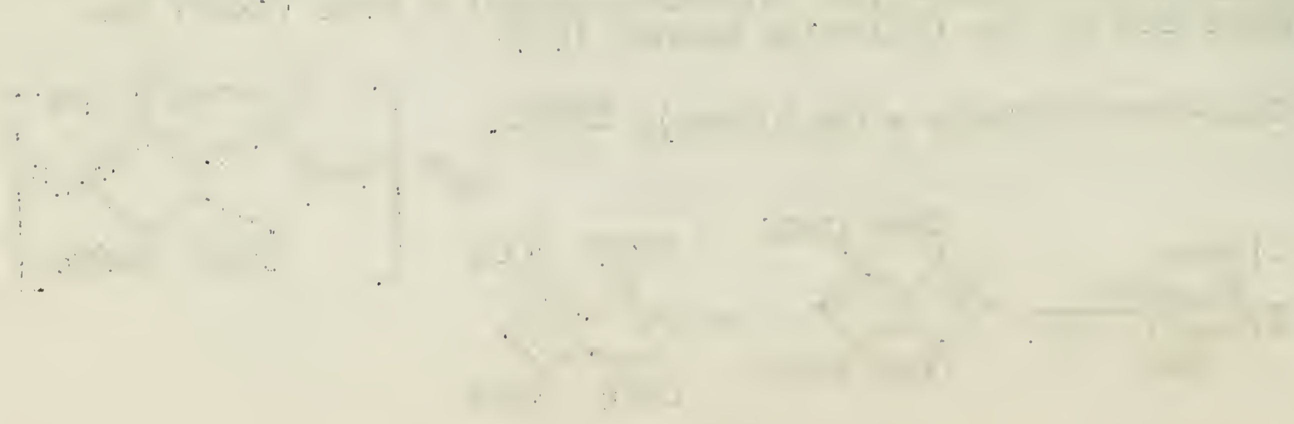
XXIII

By means of the condensation of dimethyl trichloroethylidene malonate with dimethyl malonate in the presence of sodium methoxide (23), tetrahydropentalene-1,3,4,6-tetracarboxylic acid (XXIV) has been synthesized in the following manner (24):

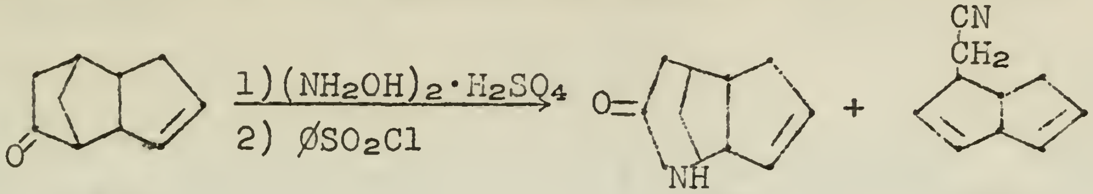


XXIV

Allylic oxidation with SeO_2 or bromination of XXIV with N-bromosuccinimide yielded no pure products.

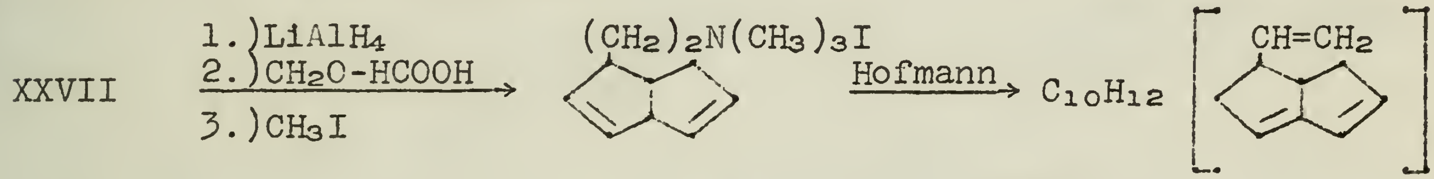


Beckmann rearrangement of the oxime of the exo-ketone XXV yielded a mixture of the lactam XXVI and the nitrile XXVII, the latter the result of a second order Beckmann rearrangement (25).



XXV XXVI XXVII

The nitrile was converted to the triply unsaturated hydrocarbon XXVIII in the following manner:

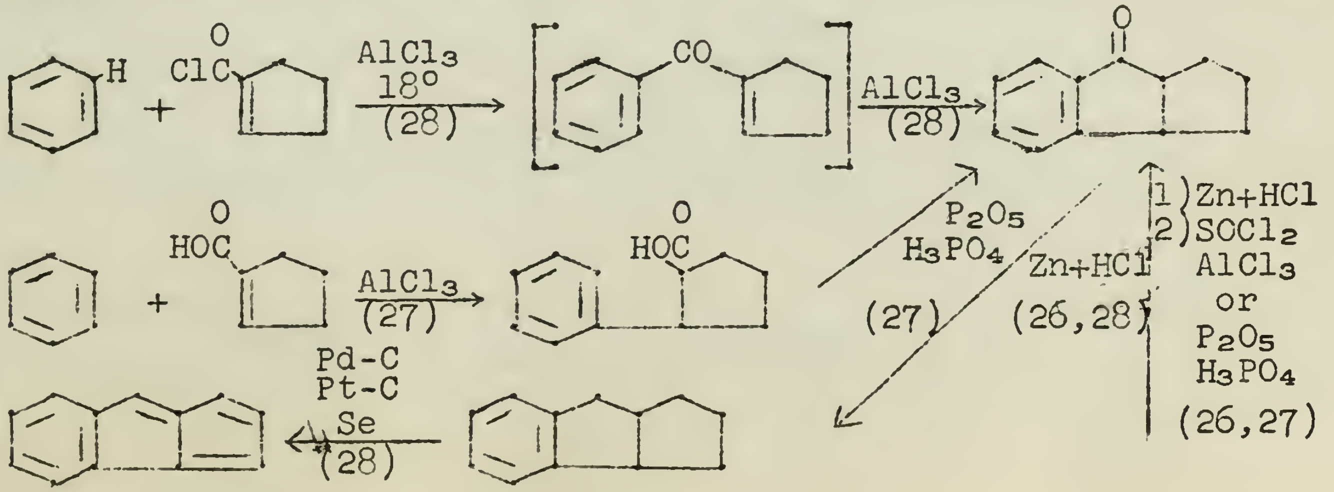


XXVIII

The IR and UV spectra of XXVIII indicated the presence of a vinyl group and conjugation of two of the double bonds. Catalytic hydrogenation of XXVIII resulted in 2-ethylbicyclo(3.3.0)octane, thus demonstrating that XXVIII did possess a vinyl substituent and the bicyclo (3.3.0)octane skeleton. The position of the two double bonds in the rings remains uncertain.

On being subjected to dehydrogenation over palladized asbestos at 300°, XXVIII yielded a substance isomeric with itself, possessing λ_{max} 252mμ, and a second, blue partially crystalline material whose UV spectrum was essentially superimposable on that of azulene. A third triply unsaturated isomer of XXVIII, prepared from the lactam XXVI by a series of reactions similar to that employed with the nitrile XXVII, also produced a deep blue oil whose UV spectrum was in general similar to that of azulene. These authors proposed that vinylpentalene was thermodynamically unstable relative to azulene.

Since the dibenzopentalene system had successfully been synthesized earlier, attempts were made to prepare benzopentalene. As in the foregoing syntheses, these attempts started with the synthesis of various compounds containing the benzobicyclo(3.3.0)octane skeleton and proceeded by either direct or indirect methods to dehydrogenate the bicyclo(3.3.0)octane nucleus. The varied syntheses of the bicyclo(3.3.0)octane skeleton and the subsequent attempts to prepare benzopentalene are summarized in the following group of reactions (26-33). (The numbers in parentheses indicate the references for each reaction.)



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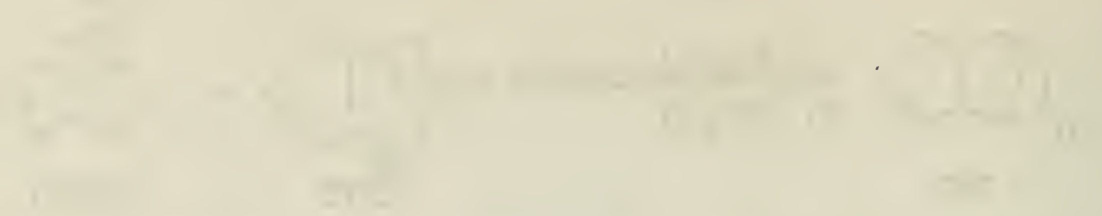

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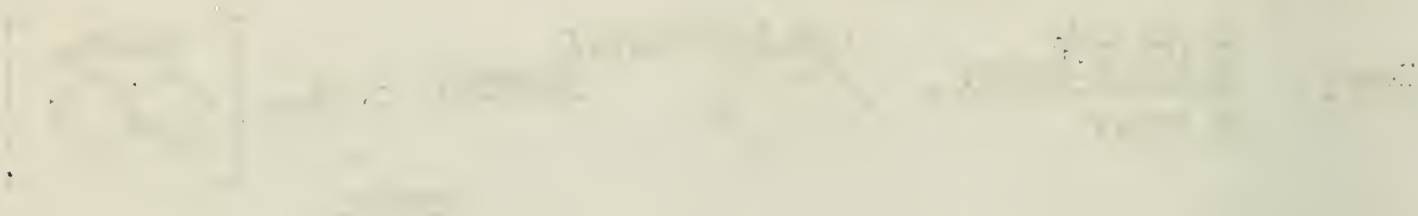

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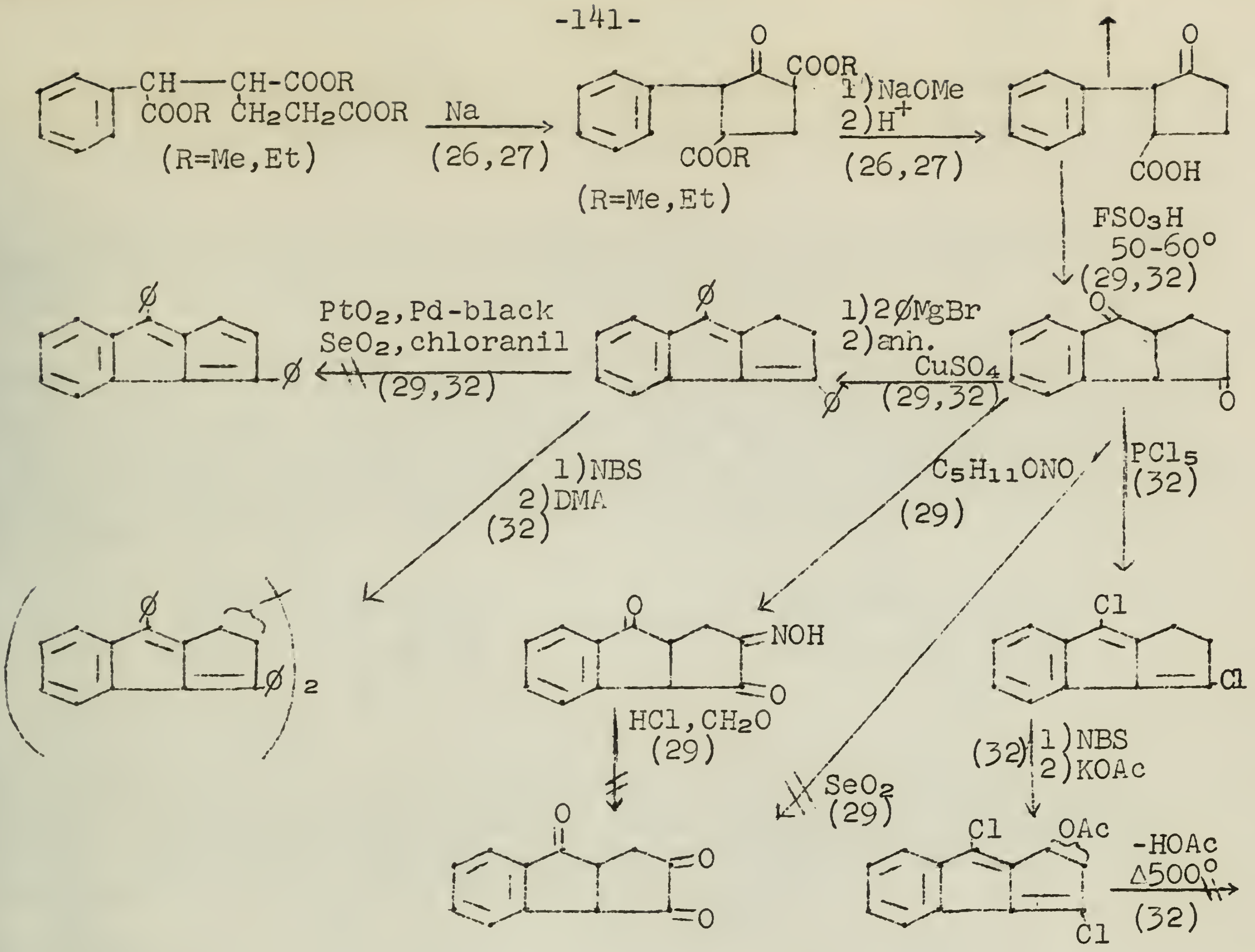
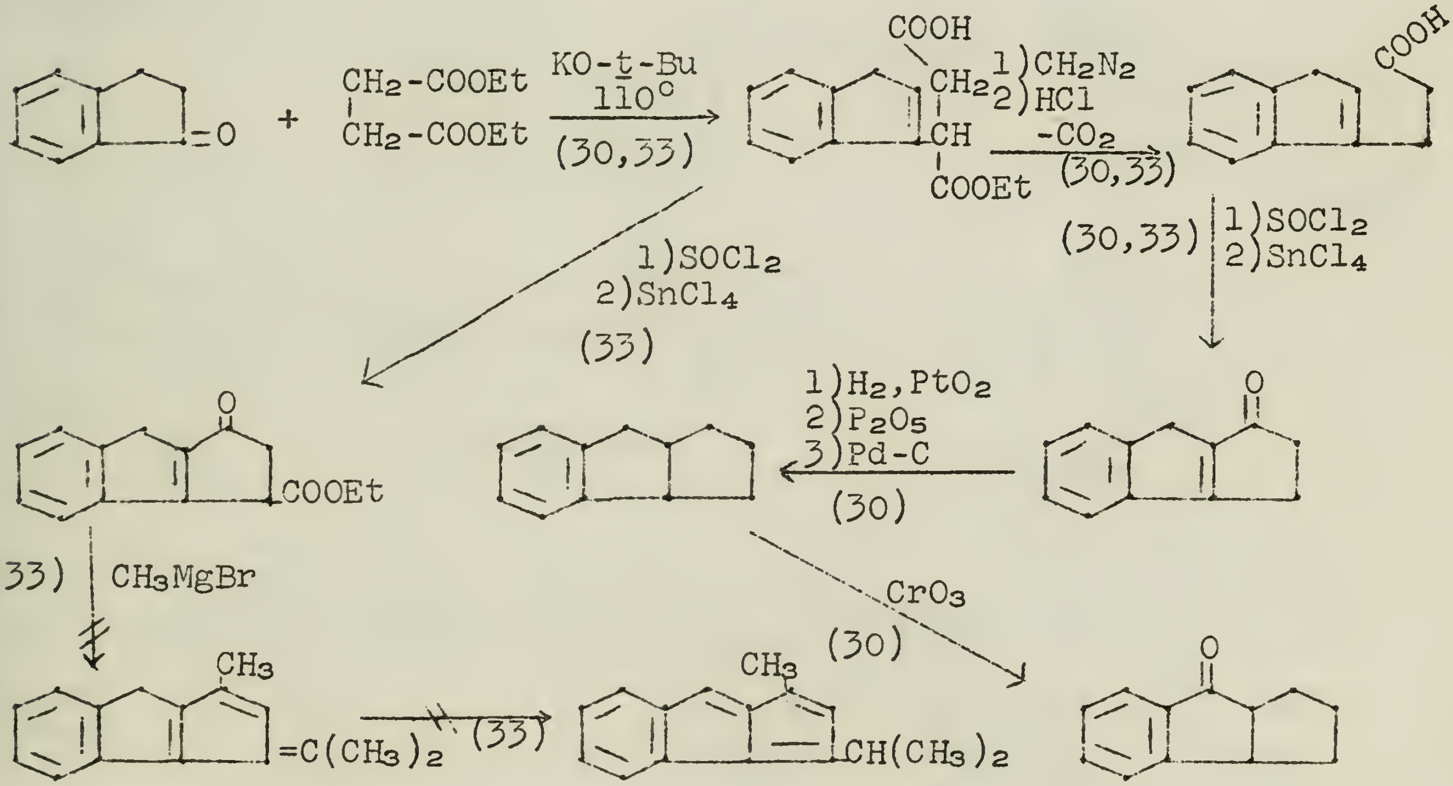
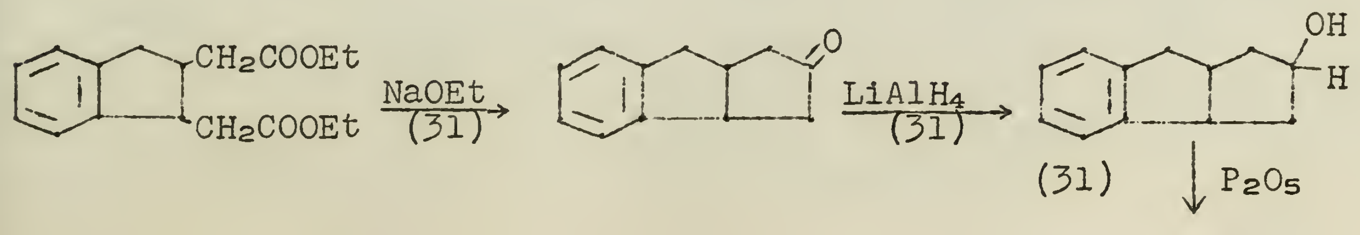
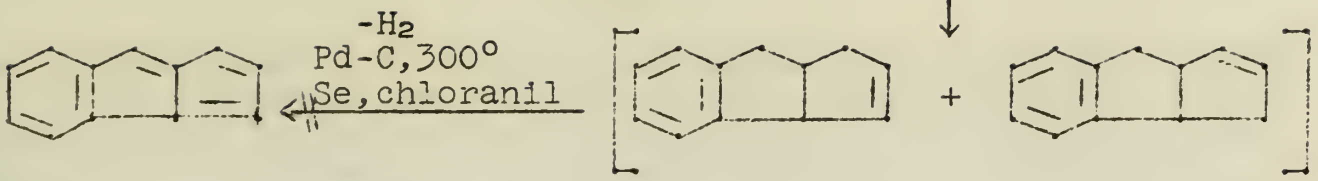

CH—CH-COOR
COOR CH2CH2COOR
(R=Me,Et)
Na
(26,27)
O
COOR
COOR
(R=Me,Et)
1)NaOMe
2)H+
(26,27)
O
COOH
FSO3H
50-60°
(29,32)
O
O
1)2ØMgBr
2)anh.
CuSO4
(29,32)
Ø
Ø
PtO2,Pd-black
SeO2,chloranil
(29,32)
Ø
Ø
1)NBS
2)DMA
(32)
Ø
Ø
2
C5H11ONO
(29)
O
NOH
O
HCl,CH2O
(29)
O
O
O
SeO2
(29)
PCl5
(32)
Cl
Cl
(32)
1)NBS
2)KOAc
Cl
OAc
Cl
-HOAc
Δ500°
(32)

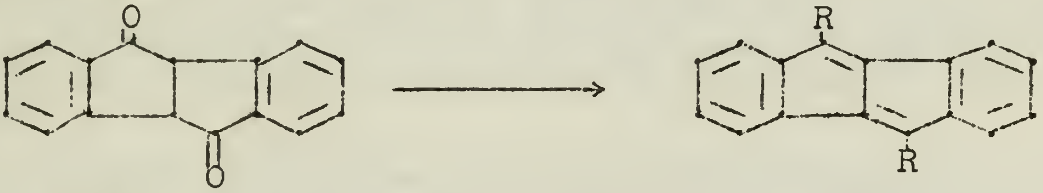

=O
+
CH2-COOEt
CH2-COOEt
KO-t-Bu
110°
(30,33)
COOH
CH2
CH
COOEt
1)CH2N2
2)HCl
-CO2
(30,33)
COOH
(30,33)
1)SOCl2
2)SnCl4
1)SOCl2
2)SnCl4
(33)
O
COOEt
O
1)H2,PtO2
2)P2O5
3)Pd-C
(30)
CrO3
(30)
O
(33)
CH3MgBr
CH3
=C(CH3)2
(33)
CH3
CH(CH3)2


CH2COOEt
CH2COOEt
NaOEt
(31)
O
LiAlH4
(31)
OH
H
(31)
P2O5



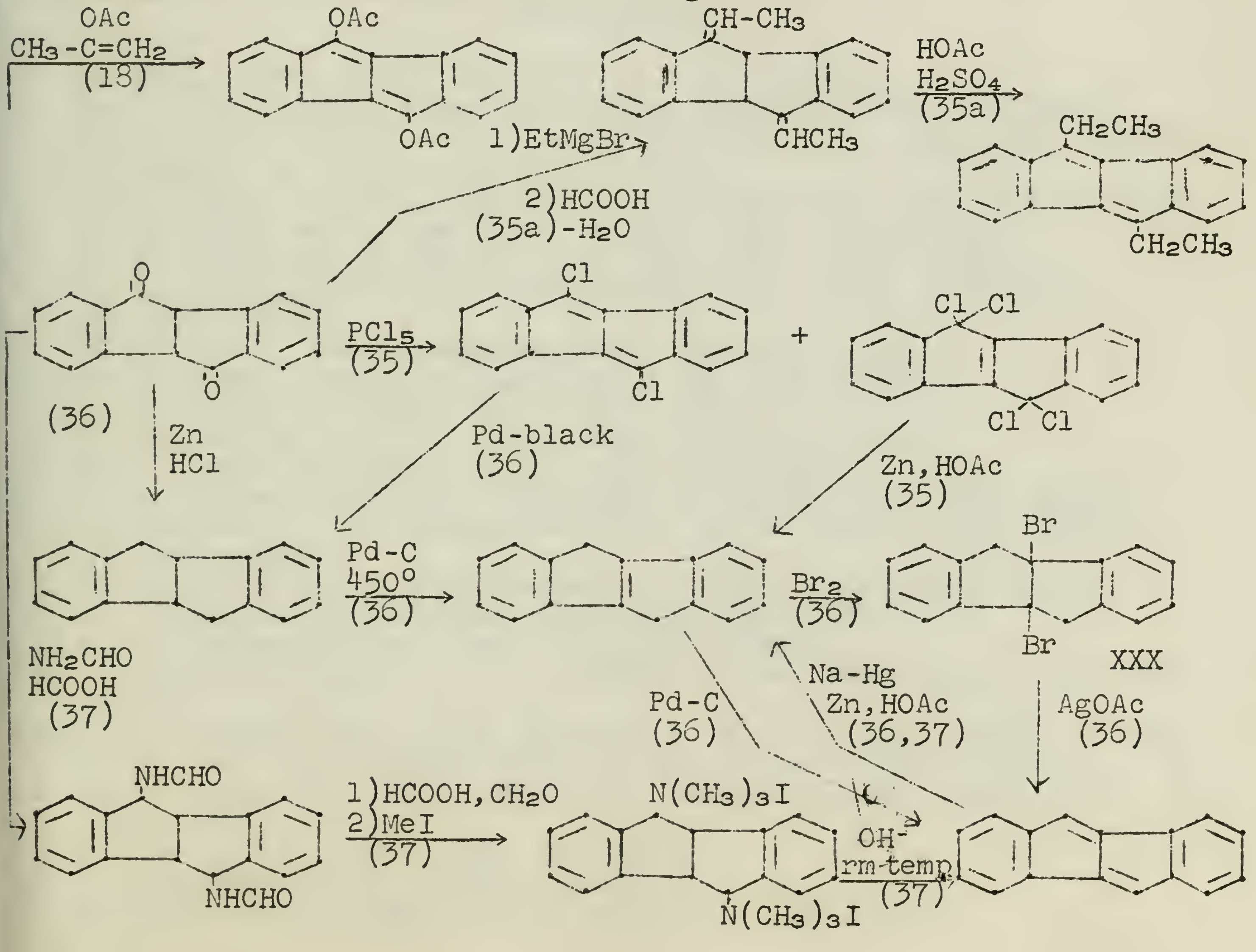
The failure to prepare benzopentalene in any of the above cases indicates the difficulty with which this system is formed, if it is formed at all, and its lack of aromatic stability.

Of the two possible isomers of dibenzopentalene, only 1,2,4,5-dibenzopentalene and a number of its 3,6-disubstituted derivatives have been synthesized. By preparing the diketone XXIX through the double ring closure of α,β-diphenylsuccinic acid with concentrated sulfuric acid, and then effecting reactions upon the two carbonyl groups, Brand was able to prepare a large number of 3,6-disubstituted-1,2,4,5-dibenzopentalenes (34).



XXIX

Brand did not succeed in isolating pure 1,2,4,5-dibenzopentalene itself, but the compound has since been prepared and its chemistry studied (18,35-37). The synthesis of this compound and some of its reactions are outlined in the following scheme.



1,2,4,5-Dibenzo-7,8-dibromo-3,6-dihydropentalene (XXX) readily loses hydrogen bromide with polymerization. Rapid fixation of any hydrogen bromide formed, as in the reaction of the dibromide with silver acetate in benzene, allowed the formation of the dibenzopentalene in good yield. The insolubility of dibenzopentalene in orthophosphoric acid (unlike azulene), its failure to form complexes with picric acid or 2,4,7-trinitrofluorenone, its ready polymerization in the presence of halogen acids, and its ready addition of bromine demonstrate its lack of aromatic stability and its tendency to react like a conjugated diene.

The UV spectrum of dibenzopentalene (λ_{max} 273,281,415mμ; ϵ= 61,000; 69,000; 15,000) has been compared to that of cis-cis-1,4-diphenylbutadiene (λ_{max} 299mμ, ϵ=30,000), which it resembles in formal structure. The 273 and 281mμ bands have been assigned to the diaryldiene system, and the presence of the long wave length band has been taken as evidence for the presence of a new chromophore, which may result through resonance interaction in the excited state of the molecule (36).

Several dihydro derivatives of 1,2,5,6-dibenzopentalene have been prepared (38), but these derivatives failed to yield the completely unsaturated 1,2,5,6-dibenzopentalene system in dehydrogenation, dehydration, ester pyrolysis or enolization experiments.

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RECENT ADVANCES IN CARBENES

Reported by R. Z. Greenley May 4, 1959

INTRODUCTION

This seminar will be devoted to the recent work done in the field of carbene chemistry with particular emphasis placed on the dihalocarbenes. Two excellent review articles are available which deal with the previous work along this line (1,2).

In accord with the nomenclature proposed by Skell (3), we will refer to carbenes as those compounds with two unshared electrons with anti-parallel spins (a singlet state). Methylenes are the diradical species, containing two unshared electrons with parallel spins (a triplet state). Those intermediates which are, as yet, inconclusive, we will call carbenes.

CARBENE FORMATION FROM HALOFORMS

In 1950 Hine presented the first sufficient evidence for dihalocarbenes (4). He proposed the following mechanism:

$$CHX_3 + OH^{\ominus} \xrightleftharpoons[\text{fast}]{k_1} CX_3^{\ominus} + HOH$$

$$CX_3^{\ominus} \xrightleftharpoons[\text{slow}]{k_2} CX_2 + X^{\ominus}$$

$$CX_2 \xrightarrow[OH^{\ominus},\ H_2O \atop k_3]{\text{fast}} CO + HCO_2^{\ominus}$$

The relative rates of reaction of the various haloforms proceeding to dihalocarbenes can be tabulated: $CHBrClF \gg CHBrCl_2 > CHBr_2Cl \sim CHCl_2I > CHBr_3 > CHCl_3 \gg CHF_3$ (5). The kinetics of the intermediate carbanion formation were studied through the use of deuterated haloforms in buffered solutions.

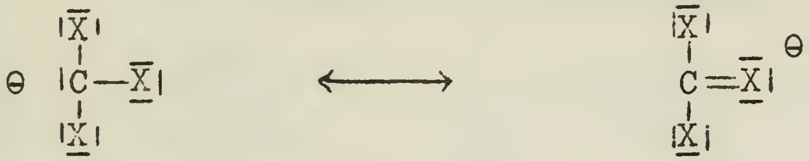
TABLE I

SUMMARY OF KINETIC DATA ON CARBANION FORMATION BY HALOFORMS IN AQUEOUS SOLUTION

Haloform	10^4K (1/mole.sec.), 0°	$\Delta H^{\ddagger}$ (kcal/mole)	$\Delta S^{\ddagger}$ (e.u.)
$CDCl_2F$	0.893	25.9	17.7
$CDBrClF$	21.0	24.3	18.3
$CDCl_3$	47.0	23.5	17.1
$CDBr_2F$	180		
$CDCl_2I$	275	22.1	15.3
$CDBrCl_2$	~290		
$CDBr_2Cl$	1435	21.3	15.6
$CDBr_3$	5790	20.3	15.0
CDI_3	6010	20.2	14.5

The apparent order, $I \sim Br > Cl > F$, in carbanion formation is in agreement with data for trihaloacetate decarboxylation (6).

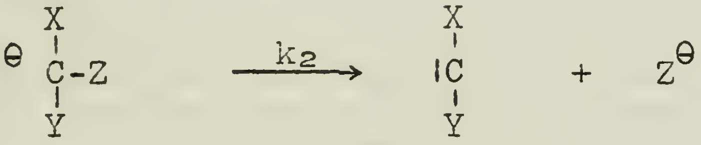
While the ease of carbanion formation of chloroform has been attributed to the electronegativity of the chlorine atoms, there appear to be three factors that might be considered in explaining why the effect of the α-halogens is almost the reverse of that expected from the inductive effect. (a) There may be repulsions among the three halogen atoms that may be relieved upon formation of the more nearly planar carbanion. But $CDBr_3$ and CDI_3 are equally reactive. Although iodine is less electronegative than bromine, its steric requirement should more than overbalance this since the replacement of chlorine by bromine does lead to a faster rate. (b) A second factor is "d-orbital resonance" for the three heavier halogens.



Hine feels that he cannot emphasize this factor since no pertinent calculations have been made for the halogen family. (c) The action of the halogen in facilitating carbanion formation may be viewed as one of lowering the free energy of the carbanion (and the transition state leading to it) by increasing the volume over which the negative charge is spread. Thus the polarizability of the halogens may show the key to the reaction series (6).

Tiers has shown through Nuclear Spin Resonance that the bulkiness of iodine has the effect of compensating for its lesser electronegativity in producing electron withdrawal from nearby groups (7).

A study of the carbanion dissociation would obviously be the next step in the series.



Hine postulated three controlling factors for this reaction: (1) the ease with which $Z^{\ominus}$ can break away, (2) the ability of X and Y to stabilize the dihalocarbene formation in the transition state, (3) the extent to which X, Y, and Z stabilize the carbanion, lowering k_2. To get some idea of these parameters, Hine used the following equation:

$$\log \frac{(k_2/k_{-1})_{CHXYZ}}{(k_2/k_{-1})_{CHCl_3}} = M_x + M_y + N_z + \log \frac{nz}{3} + \left[(c-d) \log \frac{k_1^{CHXYZ}}{k_1^{CHCl_3}}\right]$$

where:

M_x and M_y = carbene stabilization factors for the two haloforms that become part of the carbene

N_z = a constant for the halogen being lost in the transition state

$\log \frac{nz}{3}$ = a statistical factor, where nz = the number of halogens of the type being lost and 3 = the number in chloroform

(c-d) = constants relating the loss of carbanion character in the transition states leading to carbanion, (c), and dihalocarbene, (d).

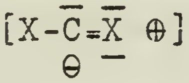
The k_1's were determined from the average deuterium kinetic isotope effect of dichlorofluoromethane and bromochlorofluoromethane: 1.75 at 0° and 1.43 at 50°. Then k_2/k_{-1} can be determined from the hydrolysis rate constant: $k_h = k_1(k_2/k_{-1})/1 + (k_2/k_{-1})$. This equation assumes that Bronsted's catalysis low holds and that changes in the energy of activation will be linear.

VALUES OF THE PARAMETERS

	0°	50°		0°	50°
M_F	+3.727	+3.193	N_{Br}	0.785	0.936
M_{Br}	-1.461	-1.131	N_I	0.118	0.486
M_I	-2.626	-2.039	(c-d)	0.299	0.196

(Since chloroform is used as the reference, N_{Cl} and M_{Cl} = 0.)

The observed order, $M_F \gg M_{Cl} \geq M_{Br} > M_I$ for carbene stabilization is attributed to the relative abilities of the four halogens to supply electrons to the deficient carbon atom.



$$[X-\underset{\ominus}{\overline{C}}=\underline{\overline{X}}\ \oplus]$$

While the order $N_{Br} \geq N_I > N_{Cl}$ is not the one most commonly observed in nucleophilic displacement reactions of saturated aliphatic halides, it has been reported on more than one occasion (8). In the reaction of bromodichloromethane and indene, it was found that the tendency for bromide ion expulsion is six times greater than that for chloride ion (9). It is probable that some of the assumptions (e.g., that the transition state has the same amount of carbanion character for each haloform) implicit in the rate equation are incorrect. The fact that c is larger than d (c-d is positive) suggests that the trihalomethyl anions have lost more carbanion character in the transition state leading to haloform than that leading to dihalocarbene (8).

In a study of salt effects on dihalocarbenes, Hine found that chloride ion slows down the basic hydrolysis of chloroform much more than bromide or iodide ions by combining with dichlorocarbene to yield haloforms:

$$CCl_2 + I^{\ominus} \longrightarrow CCl_2I^{\ominus} \xrightarrow{H_2O} CHCl_2I$$

Flourine-containing carbenes showed a poor tendency to combine with halide ions in agreement with the above "M" parameters (10).

Fluoro-carbenes were found to offer a unique series. The rate constant for the reaction of alkoxide ion with chlorodifluoromethane is too great for an S_N2 mechanism, especially since α-fluorine atoms decrease S_N2 reactivity (11). And since (a) the hydrolyses rates of bromodifluoromethane and chlorodifluoromethane ($K = 7 \times 10^{-4}$ l/mole·sec) are forty times greater than would be expected for carbanion formation, (b) non-fluoro-anions revert to haloform 10-1000 times more rapidly than they form carbenes, and (c) monofluoro anions

dissociate to carbenes 8 to 40% of the time they are formed, the difluorohaloforms are postulated to hydrolyze through a concerted α-elimination mechanism:

$$OH^{\ominus} + HCF_2Cl \longrightarrow \overset{\delta^-}{HO}\cdots H\cdots \overset{\delta^-}{CF_2}\cdots \overset{\delta^-}{Cl} \longrightarrow HOH + CF_2 + Cl^{\ominus}$$

The greater the negative charge on carbon, the more easily the halide ion is lost. The greater the extent to which halide ion is lost, the more acidic is the hydrogen being removed by the base (12,13). An alternative possibility that was not disproven is the irreversible decomposition of the anion.

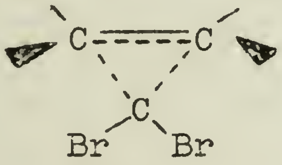
In accordance with this, the decarboxylation of chlorodifluoroacetate was also postulated to occur through a concerted mechanism:

$$ClCF_2CO_2^{\ominus} \longrightarrow \overset{\delta^-}{Cl}\cdots \overset{\delta^-}{CF_2}\cdots \overset{\delta^-}{CO_2} \longrightarrow Cl^{\ominus} + CF_2 + CO_2$$

This proposed scheme fits the experimental data very well (14,15). But, since only 80% of the reaction products were accounted for, this may need modification in the future.

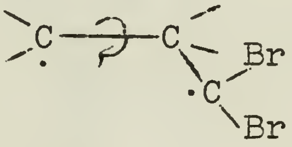
THE NATURE OF CARBENE ADDITION

It has been found that dihalocarbenes add to olefins in a stereospecifically cis manner (16,17,18). There are two possible intermediates for the reaction of dibromocarbene with 2-butene:



(I)

or

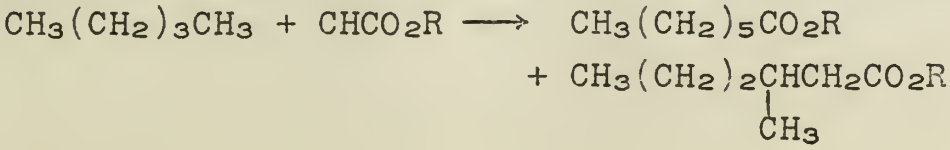


(II)

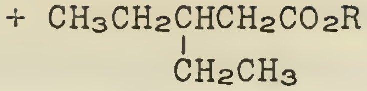
Besides the non-stereospecificity that (II) would afford (if the bond rotation is faster than radical coupling), a comparison of relative rates for radical addition ($\cdot CCl_3$) and CBr_2 addition showing a large dissimilarity rule out (II) as an intermediate. Since non-radical bromination and epoxidation are postulated to proceed through a 3-centered, electrophilic reaction, these rates were compared to CBr_2. The results favorably support (I) as the intermediate (18).

Carbethoxycarbene also adds to olefins in a stereospecifically cis manner. A comparison of its relative rates of addition with those of dihalocarbene, bromination, and radical addition again favors the three-centered intermediate (19). This type of carbene appears to be less stable than the dihalo type as it is less selective in its site of addition (20):

$$N_2CHCO_2R \xrightarrow[\text{or } \Delta]{h\nu} N_2 + CHCO_2R$$

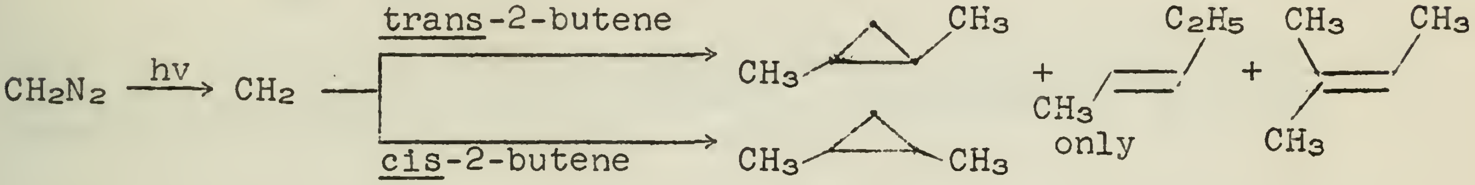


$$CH_3(CH_2)_3CH_3 + CHCO_2R \longrightarrow CH_3(CH_2)_5CO_2R + CH_3(CH_2)_2\underset{\displaystyle CH_3}{\underset{|}{C}}HCH_2CO_2R$$



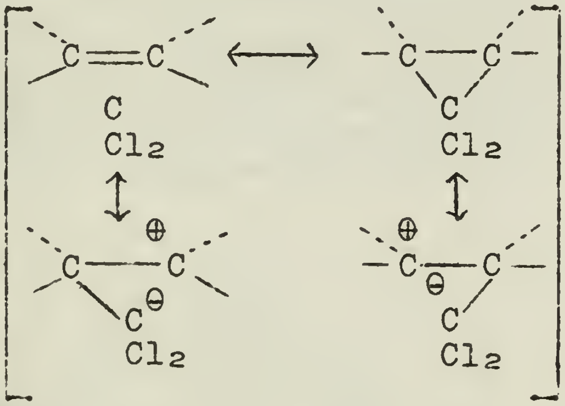
$$+\ CH_3CH_2\underset{\substack{|\\ CH_2CH_3}}{CH}CH_2CO_2R$$

Within a few percent, it is clear that carbene (from diazomethane) fails to distinguish between different types of carbon-hydrogen bonds, reacting at random with primary, secondary, and tertiary aliphatic carbon-hydrogen bonds as well as with allylic and vinyl types (21).



All the rings are stereospecifically formed, but cis-2-butene is the only olefin found so far with which carbene reacts with discrimination (16).

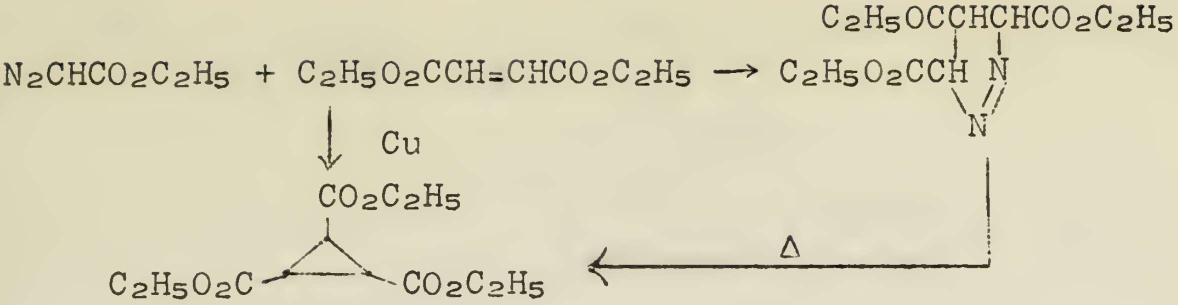
In competition experiments with dihalocarbenes and various olefins, Doering found the following relative rates of alkyl-substituted olefin reactivity: mono < sym-di < unsym-di < tri < tetra. This was rationalized in terms of the hypothetical geometry of the transition state consistent with the cis addition of carbenes. Among the several resonance structures written to suggest the less localized character of the electrons,



those with the carbon bearing the positive charge must be prominent. Thus those olefin structures which better stabilize the positive charge will lower the transition state energy and increase the rate of reaction of that olefin (22).

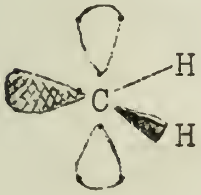
The electrophilic character of the carbenes leads to the suggestion that electron-withdrawing substituents on 1,3-butadiene would result in cyclopropane formation at the unsubstituted double bond. This has been partially substantiated by the failure of dichloro carbene to react with hexachloro-1,3-butadiene (17).

In some carbene-type reactions from diazo compounds, a pyrazoline intermediate has been ruled out by the fact that either heat or catalysis is necessary to decompose the pyrazolines (23):

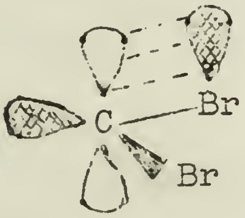


[see also (47)]

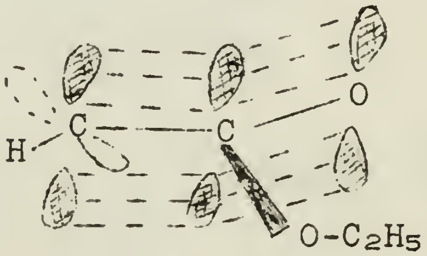
From the above data, spectroscopic evidence, and quantum mechanical calculations, the following electronic configurations have been postulated for various carbenes (19,24):



CH_2



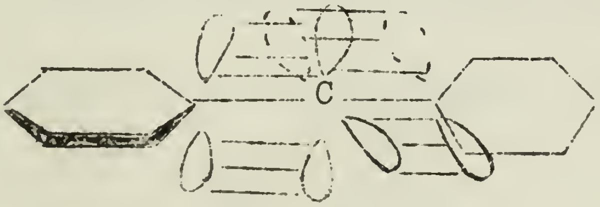
CBr_2



$CHCO_2C_2H_5$

(▨ : filled orbital)

Diphenylmethylene, produced photochemically from diphenyldiazomethane, does not react stereospecifically with 2-butene, follows a radical reactivity sequence, reacts with oxygen to give benzophenone (3,25), and in its addition reaction with (-)menthyl acrylate yields a totally inactive product (26). Thus it was assigned this diradical configuration (3):



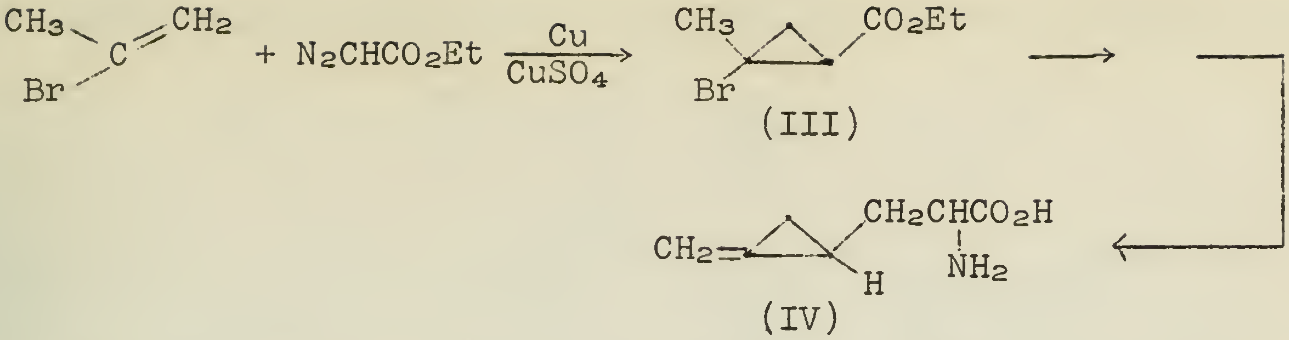
PHYSICAL DATA

Carbene, produced photochemically form ketene in the gas phase, substitutes into the primary and secondary carbon-hydrogen bonds of propane and butane in the ratio 1:1.7 at room temperature (27). Besides other reactions, carbene stereospecifically (28) forms cyclopropane rings which are extremely energy rich and either isomerize to a linear olefin or are deactivated through collisons (29).

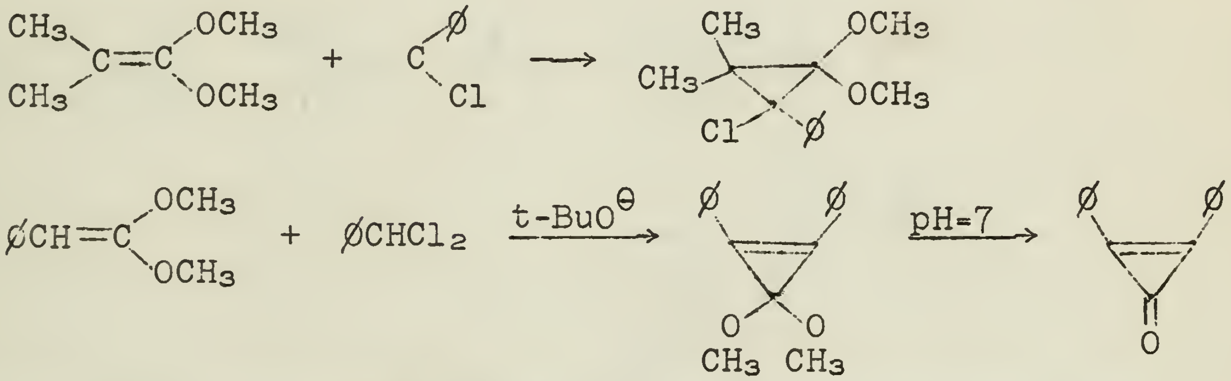
Molecular orbital calculations have placed the H-C-H angle in CH_2 between 90° and 140° depending on whether this is applied to carbene or methylene (30,31,32).

SYNTHETIC APPLICATIONS

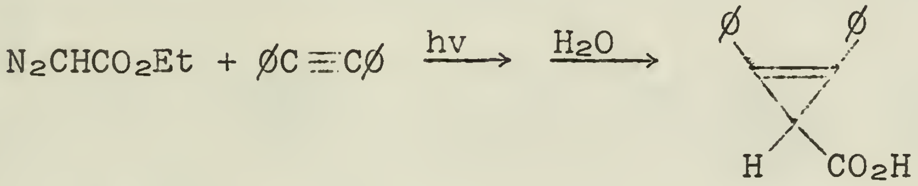
In addition to being a novelty, carbenes have found their place as a synthetic tool in the formation of cyclopropanes.



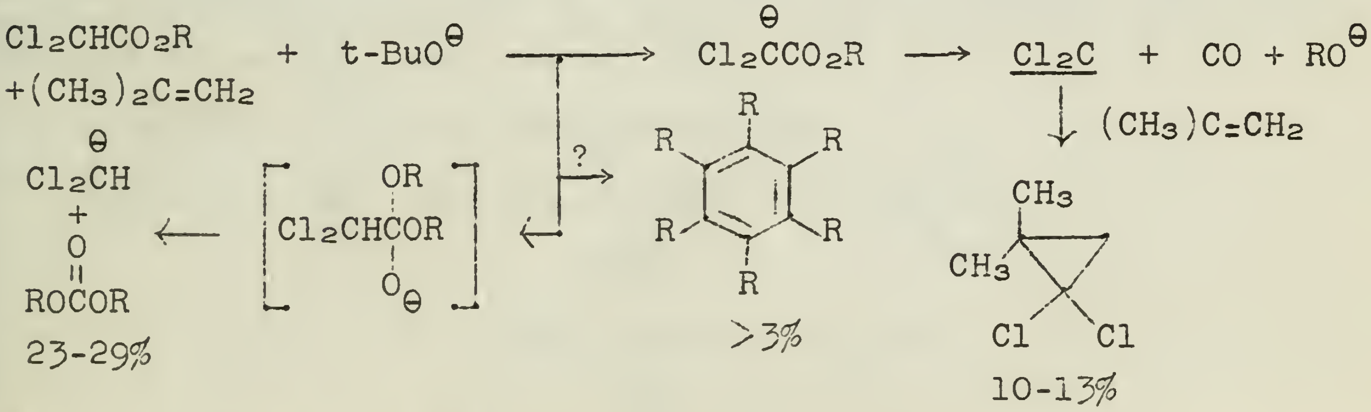
Compound (III) was used as an intermediate in the synthesis of Hypoglycin A (IV)(33). Carbene reaction with ketene acetals proved to be worthwhile (34,35):



Another diphenylcyclopropene was also prepared (36):

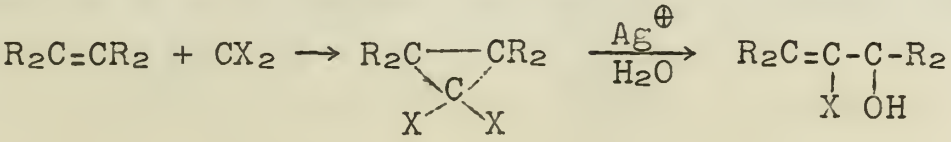


The mechanism of a carbene and isobutylene was partially shown to be (37):

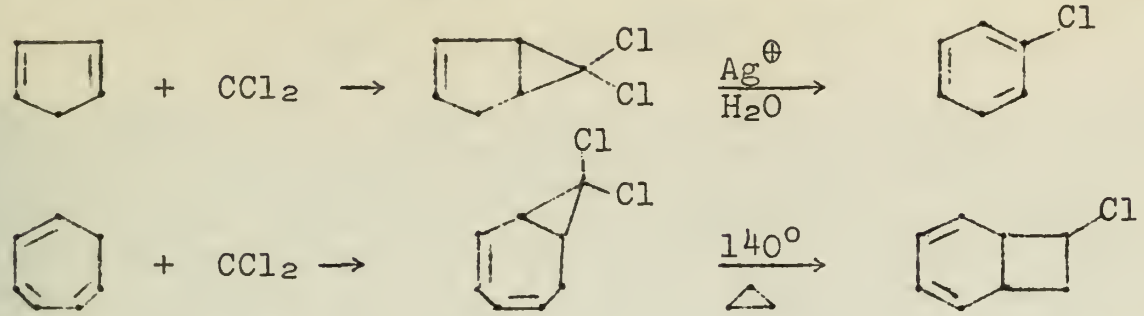


where R = t-Bu and R' = -CO_2(t-Bu). The yield of cyclopropane can be increased to 55% by using the trihaloester.

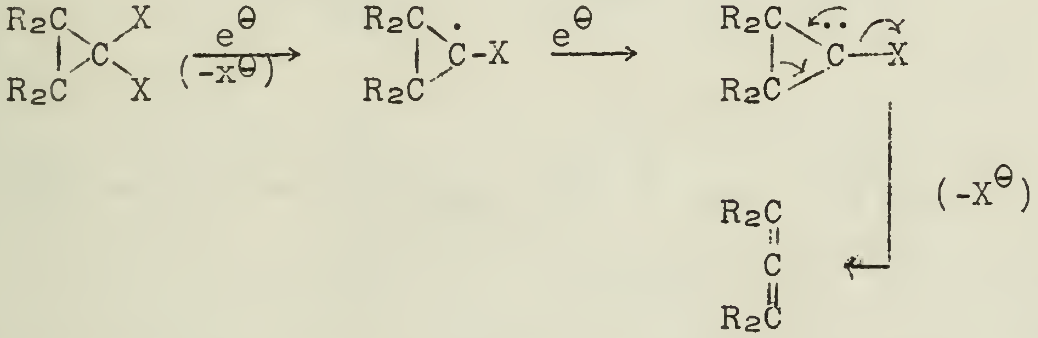
Skell has shown a sequence of general reactions for extending a carbon chain through the insertion of a halogenated carbon atom between the double bonded carbons (38):



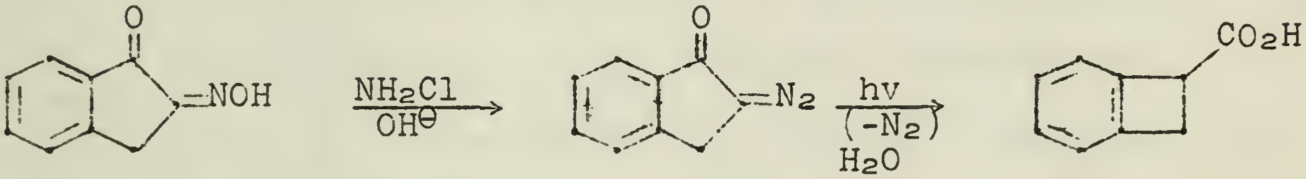
This scheme was used ter Borg to synthesize conjugated rings (39):



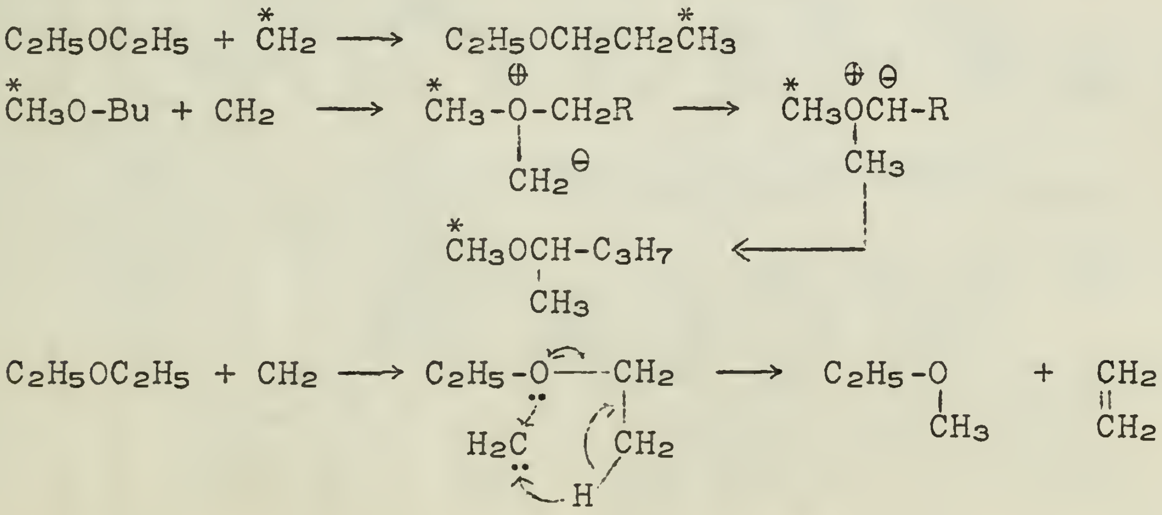
Doering and La Flamme have rearranged the cyclopropyl ring through the use of magnesium or sodium to form allenes (40):



The reduction of oximes or hydrazones to the corresponding diazo compounds can lead to a carbene source (41,42). For example,



The reaction of carbene with ethers gives two groups of reaction products. One is formed through substitution of the hydrogen atom on the carbonhydrogen bond of the ether by the carbene, the other results in the cleavage of the ether molecule through an attack by the carbene on the ether oxygen (43).

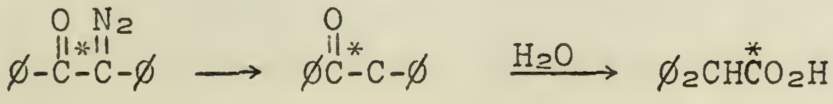


$$C_2H_5OC_2H_5 + \overset{*}{C}H_2 \longrightarrow C_2H_5OCH_2CH_2\overset{*}{C}H_3$$

$$\overset{*}{C}H_3O\text{-}Bu + CH_2 \longrightarrow \overset{*}{C}H_3\text{-}\underset{CH_2^{\ominus}}{\overset{\oplus}{O}}\text{-}CH_2R \longrightarrow \overset{*}{C}H_3\overset{\oplus}{O}\underset{CH_3}{\overset{\ominus}{C}}H\text{-}R \longrightarrow \overset{*}{C}H_3O\underset{CH_3}{C}H\text{-}C_3H_7$$

$$C_2H_5OC_2H_5 + CH_2 \longrightarrow C_2H_5\text{-}\underset{H_2\ddot{C}}{\ddot{O}}\text{—}\underset{\underset{H}{CH_2}}{CH_2} \longrightarrow \underset{CH_3}{C_2H_5\text{-}O} + \underset{CH_2}{\overset{CH_2}{\|}}$$

Franzen has shown a carbene type of rearrangement (44):

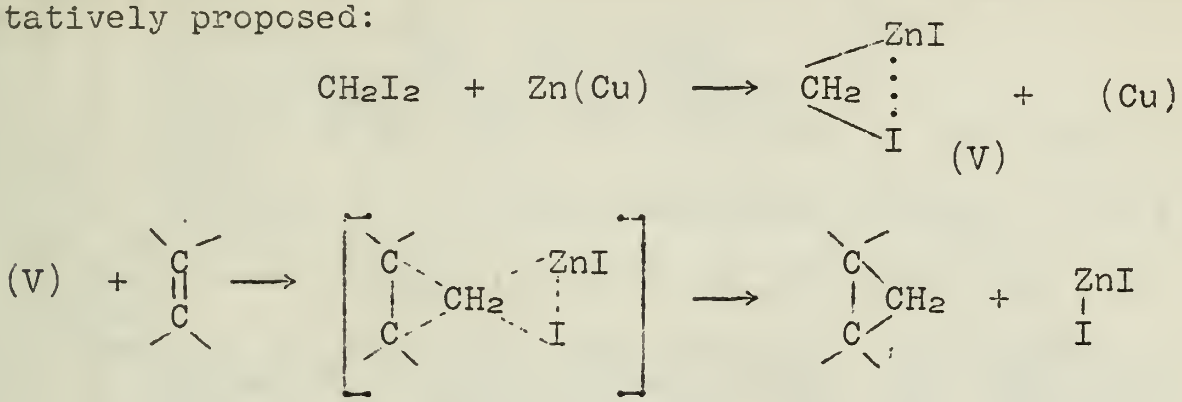


$$\varnothing\text{-}\overset{O}{\overset{\|}{C}}\text{-}\overset{*}{\overset{N_2}{\overset{\|}{C}}}\text{-}\varnothing \longrightarrow \varnothing\overset{O}{\overset{\|}{C}}\text{-}\overset{*}{C}\text{-}\varnothing \xrightarrow{H_2O} \varnothing_2CH\overset{*}{C}O_2H$$

A new synthesis of cyclopropanes has been shown (45,46).

$$CH_2I_2 + Zn(Cu) \xrightarrow{Et_2O} (V) + (Cu)$$

This complex, (V), reacts smoothly with cyclohexene to give a 48% yield of bicyclo[4.1.0]heptane. In many respects (V) follows dihalocarbenes in its method of reaction in that it attacks only double bonds, gives cis additions, no isomerization of products, and that a high electron density at the double bond increases the yields and rates. Peculiar to (V) is that it offers large steric requirements and it has not been proven that copper has no catalytic effect. In accordance with these qualifications, the following mechanism has been tentatively proposed:


CH₂I₂ + Zn(Cu) ⟶ CH₂ ZnI I + (Cu)
(V)
(V) + C C ⟶ C CH₂ ZnI C I ⟶ C CH₂ C + ZnI I

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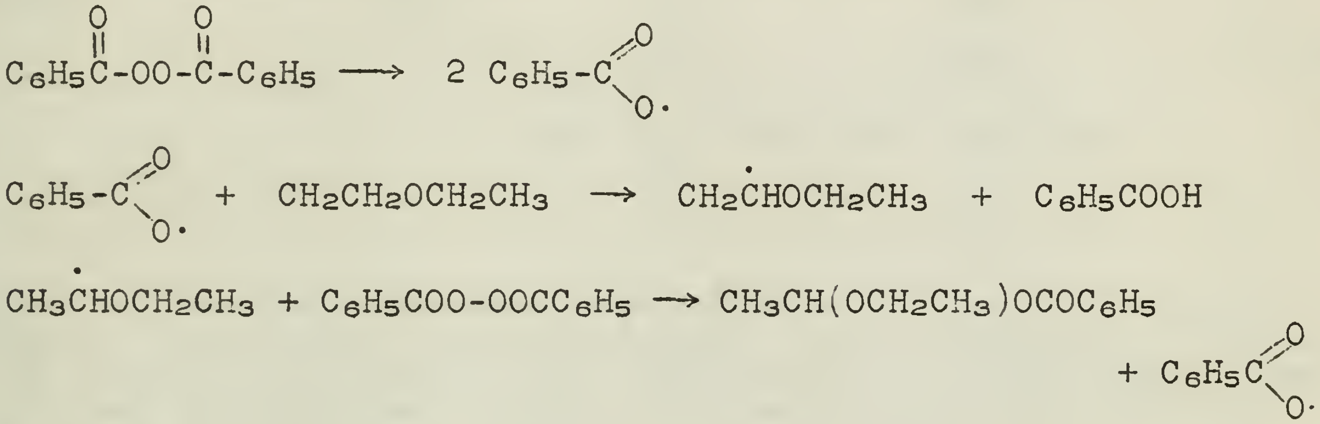
NUCLEOPHILIC ATTACK ON DIACYL PEROXIDES

Reported by R. G. Smith May 7, 1959

INTRODUCTION

The decomposition of benzoyl peroxide in various solvents has been the subject of an extensive investigation in the last two decades. The rate of decomposition was found by Bartlett (1,2) to vary widely with solvent. Thus, at 80° for solutions .197 m in benzoyl peroxide the amount of decomposition is 13% in one hour in carbon tetrachloride, 77% in one hour in pyridine, 75% in 10 minutes in diethyl ether and 87% in 10 minutes in o-cresol. The reaction is explosive in aniline under these conditions.

The rate constants were found to increase with increasing peroxide concentration and the reaction order was also found to vary with solvent. In most cases the rate variation has been satisfactorily explained by postulating induced chain decomposition. Thus the experimental data for the decomposition of benzoyl peroxide in diethyl ether is consistent with the following mechanism (33).



$$C_6H_5\overset{\overset{O}{\|}}{C}-OO-\overset{\overset{O}{\|}}{C}-C_6H_5 \longrightarrow 2\ C_6H_5-C\begin{matrix}\nearrow O\\ \searrow O\cdot\end{matrix}$$

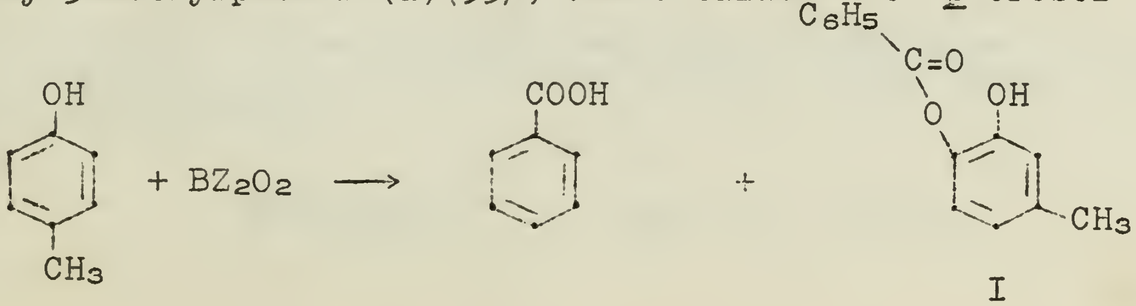
$$C_6H_5-C\begin{matrix}\nearrow O\\ \searrow O\cdot\end{matrix} + CH_2CH_2OCH_2CH_3 \longrightarrow CH_2\dot{C}HOCH_2CH_3 + C_6H_5COOH$$

$$CH_3\dot{C}HOCH_2CH_3 + C_6H_5COO-OOCC_6H_5 \longrightarrow CH_3CH(OCH_2CH_3)OCOC_6H_5 + C_6H_5C\begin{matrix}\nearrow O\\ \searrow O\cdot\end{matrix}$$

The third step in this reaction scheme may be regarded as either radical displacement on oxygen or radical addition to a carbonyl of the peroxide followed by O-O bond cleavage. Inhibitors such as styrene reduce the rate in diethyl ether to essentially the same as the rate in unreactive solvents such as carbon tetrachloride (30).

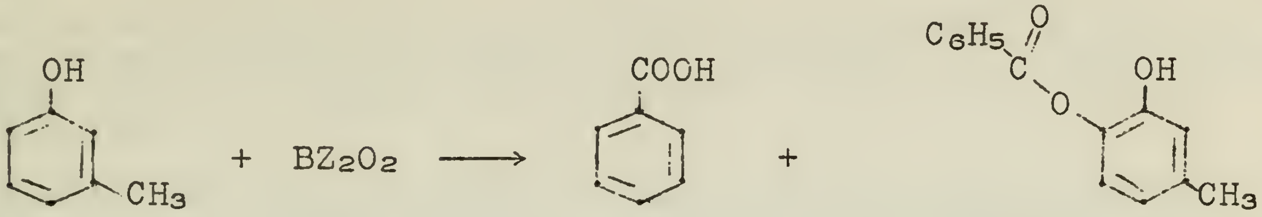
DIACYL PEROXIDE REACTION WITH PHENOLS

Walling (25) has studied the phenol-peroxide reaction and has concluded that this reaction involves nucleophilic attack by the phenol on the peroxide and does not involve radicals. Product studies have been carried out by Cosgrove and Waters (28,29) by refluxing equimolecular amounts of phenol and peroxide in chloroform. Phenols with free o-positions are found to give catechol monobenzoates (in yields from 15-35%) and benzoic acid. Benzoic acid (70%) and 2-benzoyloxy-5-methylphenol (I)(35%) are obtained from p-cresol.



I

The same products are obtained from m-cresol in yields of 67% and 17% respectively. Phenols di-substituted in the o-positions are found to yield diphenoquinones as the major product. The products from 2,6-dimethylphenol were identified as benzoic acid (86%), 3,5,3',5'-tetramethyl-4,4'-dihydroxybiphenyl (III)(10%), 3,5,3',5'-tetramethyldiphenoquinone, (II) (50%), and 2,6-dimethyl-4-benzoyloxylphenol (IV)(10%).



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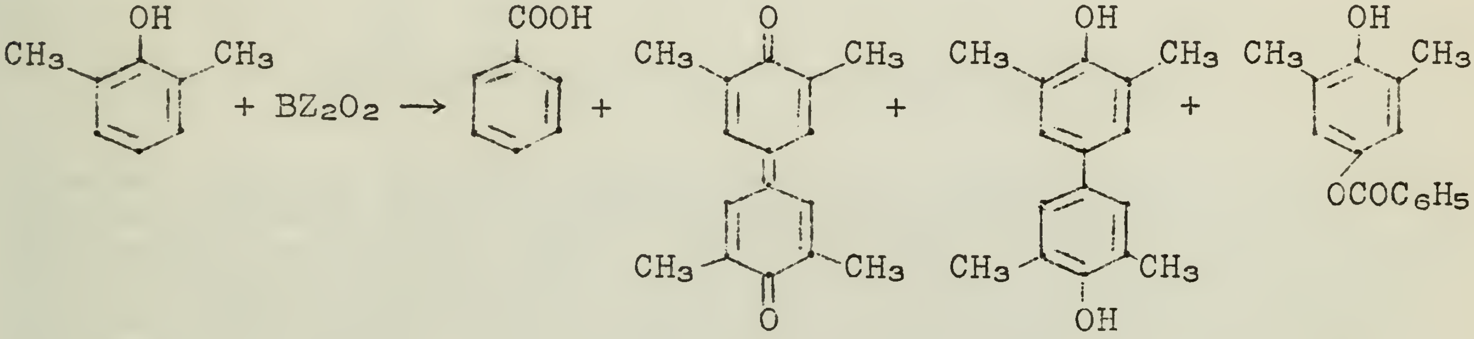
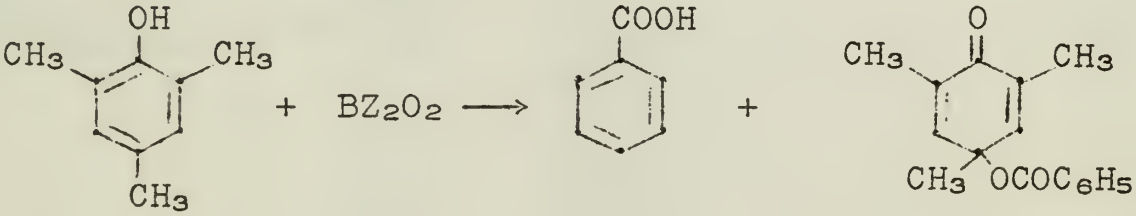


II III IV

Walling (25) has isolated the diphenoquinone (II) in 62% yield by running the reaction in refluxing benzene and in 52% yield by allowing the reaction to stand at room temperature for three weeks. The reaction was also carried out with 2,6-dimethoxyphenol (79%) and with 2,6-diisopropylphenol (65%).

The products from 2,4,6-trimethylphenol were benzoic acid (53%) and 2,4,6-trimethyl-4-benzoyloxycyclohexa-2,5-dienone (V) in 90% yield.



V

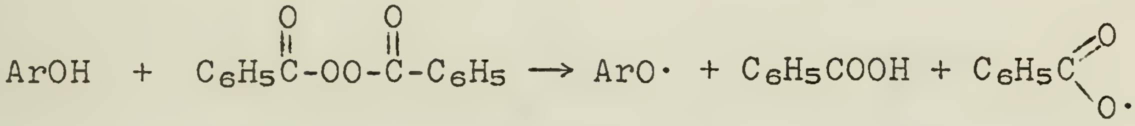
The reaction did not occur with 2,6-di-t-butyl-4-methylphenol or with 2,4,6-tri-t-butylphenol.

The kinetics of the reaction have been investigated for several phenols by Walling (25) and by Batten (26,27). Both authors report a second order rate law.

$$-\frac{d[\text{Peroxide}]}{dt} = k_2\,[\text{Peroxide}]\,[\text{Phenol}]$$

At very low phenol concentrations in reactive solvents such as dioxane a retarding effect is noted (26), which is replaced by an accelerating effect at higher phenol concentrations. In unreactive solvents no retarding effect is observed. The retarding effect can be explained as suppression of induced chain decomposition by reaction between benzoyloxy radicals and the phenol to produce phenoxy radicals which are regarded as incapable of initiating peroxide decomposition.

Batten (26) has presented evidence that the phenol-peroxide reaction is a non-chain reaction. Typical inhibitors such as _p_-benzoquinone, anthracene, styrene and oxygen were shown to have no effect on the rate of the reaction. Light was also shown to have no effect. Consequently Batten has proposed a non-chain radical forming process as the rate controlling step. The reaction is formulated as transfer of the phenolic hydrogen atom to a carbonyl of the peroxide, producing radicals which then dimerize to products.



$$ArOH + C_6H_5\overset{O}{\overset{\|}{C}}\text{-OO-}\overset{O}{\overset{\|}{C}}\text{-}C_6H_5 \longrightarrow ArO\cdot + C_6H_5COOH + C_6H_5C\begin{matrix}\diagup O \\ \diagdown O\cdot\end{matrix}$$

However, Walling (25) has investigated the reaction further and has obtained evidence which appears to rule out radicals of any sort. Thus iodine is found to have no effect on the rate or on the products. Also, no carbon dioxide is evolved in the reaction with either benzoyl peroxide or with acetyl peroxide. Since Szwarc (31) has shown that acetoxy radicals lose oxygen almost immediately on formation and before they can react with even the most reactive molecules such as iodine this fact would indicate that acetoxy radicals were not present.

Walling has also investigated the effect of phenol structure on rate by running the reaction in benzene at 30° with excess phenol (Table II). Solvent effects for the reaction with _m_-cresol at 30° are recorded in Table III.

Table II

Substituent	$k_2 x 10^7$
2,4,6-tri-t-butyl	.1
none	5.7
p-Cl	7.2
m-CH_3	27.4
p-Br	35.8
2,6-CH_3	78.0
p-CH_3	106.8
2,6-OCH_3	267.4
p-OCH_3	9021

Table III

Solvent	$k_2 x 10^7$
Nitrobenzene	33.7
Benzene	27.4
Chloroform	27.3
Pyridine	26.0
Acetophenone	8.3
Acetone	3.4
Ethanol	2.8
Acetic Acid	.7

The conclusions which can be drawn from the above data are:

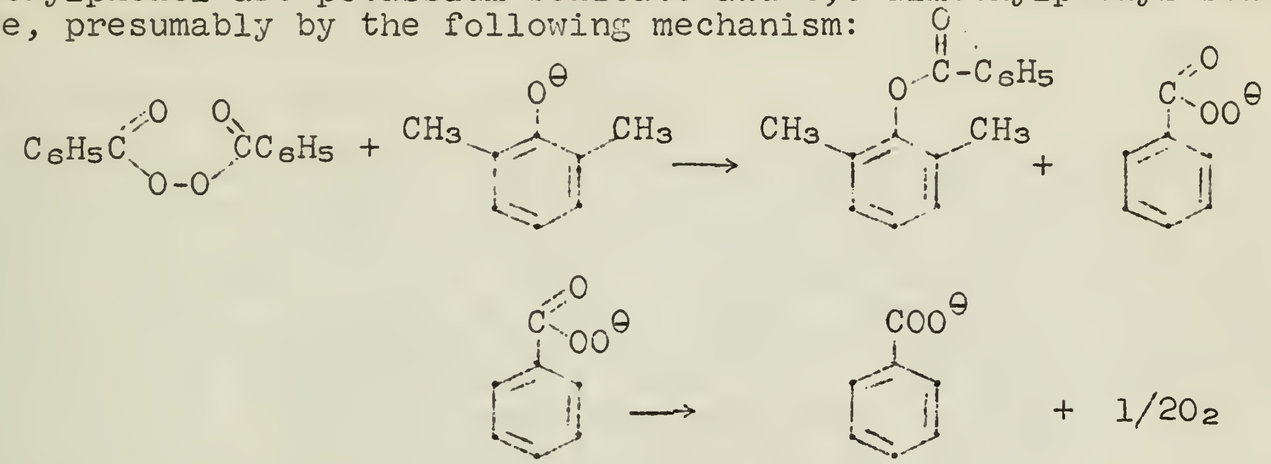
1. Strongly electron-supplying p-substituents accelerate the reaction although there is no Hammett σ_p relation. This seems to indicate that the phenol is behaving as an nucleophilic reagent.

2. Steric factors are operative which suggests that the phenolic hydroxyl is involved in the rate controlling step.

3. Solvent effects cannot be correlated with any common solvent properties. However, solvents capable of hydrogen bonding cause a marked rate depression.

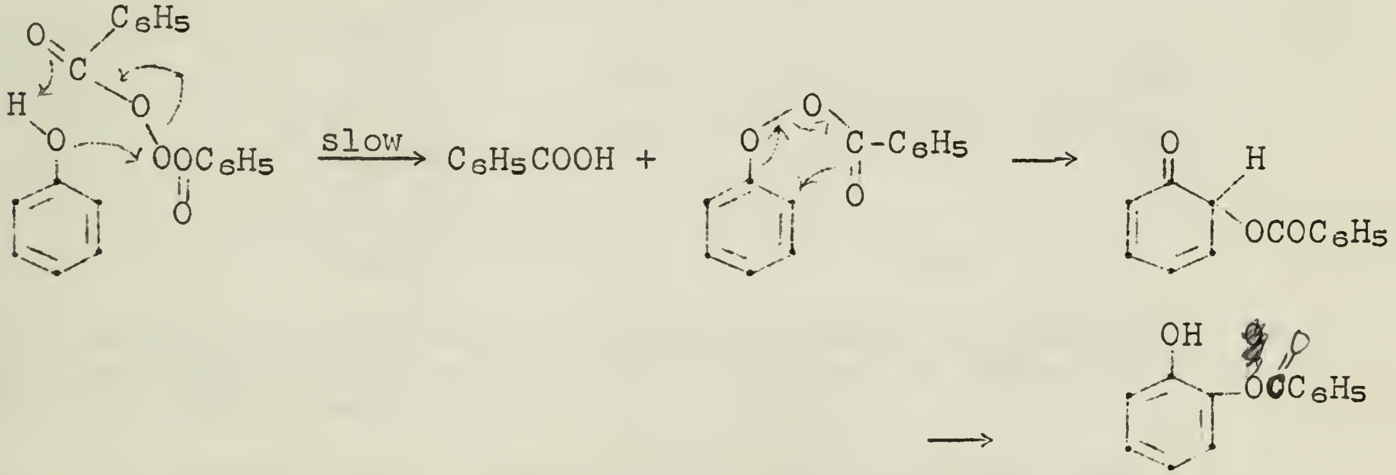
4. The reaction is not subjected to acid or base catalysis since the rate in pyridine is similar to rates in other aromatics and the rate is very low in acetic acid.

With stronger bases the reaction is found to follow a different course. The products obtained from the potassium salt of 2,6-dimethylphenol are potassium benzoate and 2,6-dimethylphenyl benzoate, presumably by the following mechanism:

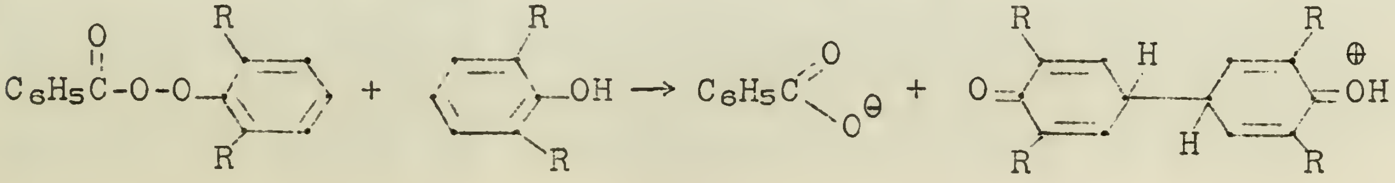


The reaction was also investigated with o-deuterated phenols with both benzoyl peroxide and acetyl peroxide. All the experiments showed an isotope effect $k_H/k_D = 1.32 \pm .03$. Activation parameters were determined for m-cresol ($\Delta H^{\ddagger} = 17.4$ kcal, $\Delta S^{\ddagger} = -26.7$ eu.) and for p-methoxyphenol ($\Delta H^{\ddagger} = 15.3$ kcal, $\Delta S^{\ddagger} = -22.3$ eu.).

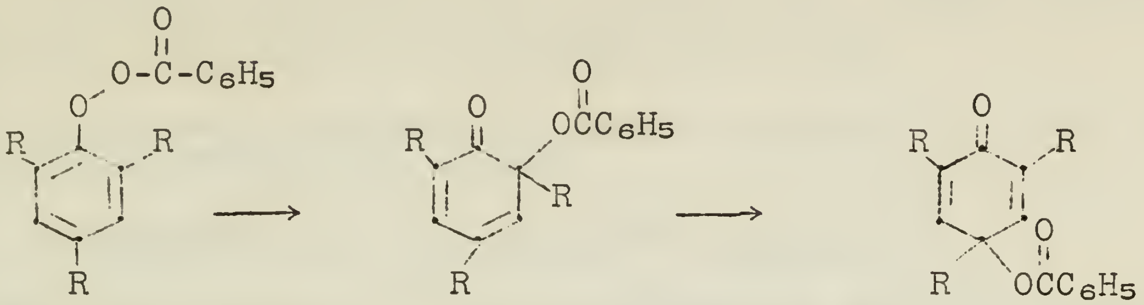
On the basis of the results reported above Walling has proposed a molecular mechanism for the phenol-peroxide reaction. For phenols with free o-positions the reaction can be regarded as displacement of phenolic hydrogen by the peroxide.



The formation of diphenoquinones from 2,6-disubstituted phenols can also be formulated as involving the same intermediate, followed by electrophilic attack on another phenol molecule, proton loss, and tautomerization to the hydroquinone and then further oxidation.



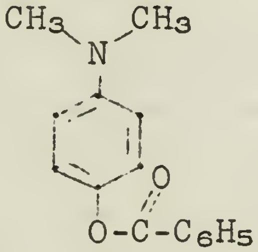
The formation of benzoyloxydienones from 2,4,6-trisubstituted phenols can be formulated similarly by a mechanism similar to the *p*-Claisen rearrangement.



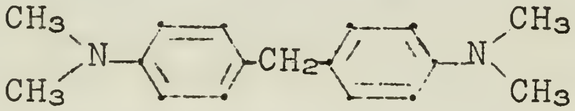
DIACYL PEROXIDE REACTION WITH AMINES

The reaction between benzoyl peroxide and dimethylaniline has been studied by Horner (11-17), Imoto (7-10) and by Walling (4). The reaction has also been reviewed by Walling (5). Although benzoyl peroxide does react with primary and secondary amines relatively little work has been done on these systems. The reaction mixture in the case of dimethylaniline has been shown to initiate polymerization and to take up oxygen and nitric oxide (11). The polymers produced by the reaction under nitrogen have been shown to contain 4-5% oxygen which is recoverable as benzoic acid on hydrolysis (12,7). The polymers were also shown to contain no nitrogen.

A product study of the benzoyl peroxide-dimethylaniline reaction at room temperature in chloroform under nitrogen has been carried out by Horner (15). The products found after aqueous treatment of the reaction mixture were (in moles per mole of peroxide decomposed) benzoic acid (1.81), formaldehyde (0.34), chloride ion (0.26), monomethylaniline (0.65), *p*-benzoyloxydimethylaniline VII (0.17) and trace amounts of *p*,*p*-di-(dimethylamino)-diphenylmethane VIII.



VII



VIII

The reaction was run with a five-fold excess of dimethylaniline, and two moles of the aniline were consumed for every mole of peroxide decomposed.

The reaction was found to obey a second order rate law (13) although Walling (4) has noted a small increase in rate constant with increasing peroxide concentration. Electron-donor groups on

$$-d\frac{[\text{Peroxide}]}{dt} = k_2\,[\text{Peroxide}][\text{amine}]$$

the amine were found to have a strong accelerating effect on the reaction. Thus, the half-life of 0.01*M* peroxide in the presence of 0.01*M* amine in chloroform at 20° is 5 minutes for *p*-methyldimethylaniline, 13 minutes for dimethylaniline and 6 days for *p*-cyanodi-

methylaniline (13). Electron-withdrawing groups on the peroxide were found to accelerate the reaction and a Hammett $\sigma\rho$ plot with $\rho = 0.181$ was obtained. This result is in marked contrast with Swain's work (30) on the thermal decomposition of substituted benzoyl peroxide in dioxane. For this reaction electron-withdrawing groups were found to retard the reaction and ρ was found to be -0.38.

In polymerizable monomers the rate of polymerization has been shown to follow the rate law (4,9):

$$-\frac{d[\text{monomer}]}{dt} = k\ [\text{Peroxide}]^{1/2}\ [\text{amine}]^{1/2}$$

Such a rate law requires an initial bimolecular radical forming process. Horner has shown that oxygen causes a rate depression and also permits the formation of titratable peroxides since when the reaction is run to completion under oxygen a quantitative recovery of benzoic acid is obtained while the peroxide titre remains high (15, 17). The peroxide formed in this reaction however was not identified.

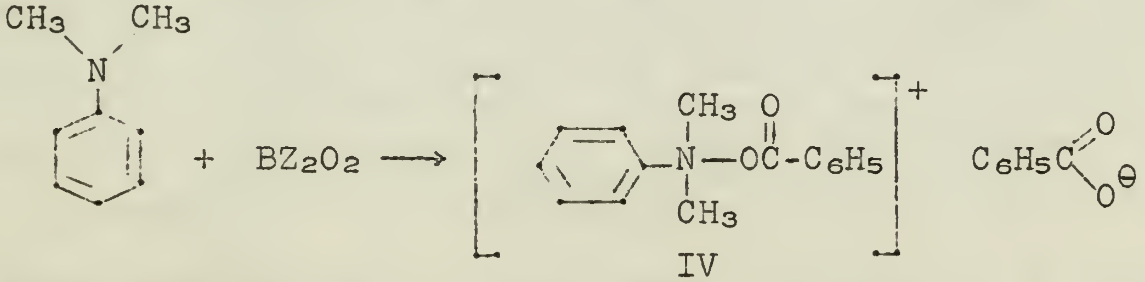
Walling (4) has recently studied the effect of various solvents on the reaction run at 0° with excess dimethylaniline (Table IV).

Table IV

Solvent	$k_2 \times 10^{14}$
Pyridine	120
Chloroform (under N_2)	19
Chloroform (under O_2)	5.2
Benzene	15.4
Ethanol	9.4
Styrene	2.8
Acetone	2.1

Acetic acid was found to depress the rate in chloroform to about the same as the rate in acetone and small amounts of benzoic acid were shown to have no effect on the reaction. Activation parameters were also evaluated for the reaction and found to be $\Delta H^{\ddagger} = 11.0$ kcals and $\Delta S^{\ddagger} = -9.9$ e.u. The system was found to have a very low efficiency of initiation of polymerization and the efficiency was found to decrease with increasing temperature (0.25 at 0° and 0.10 at 80°).

Walling (4) has proposed nucleophilic attack by the amine on the peroxide to form a quaternary hydroxylamine derivative IX as the initial rate controlling reaction.

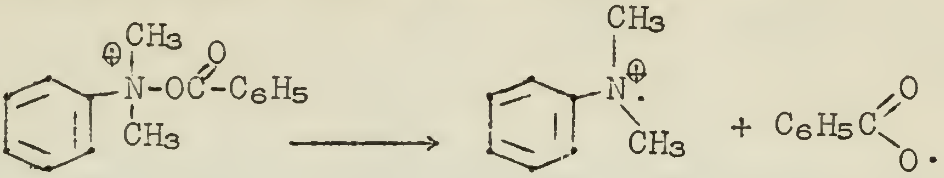


IV

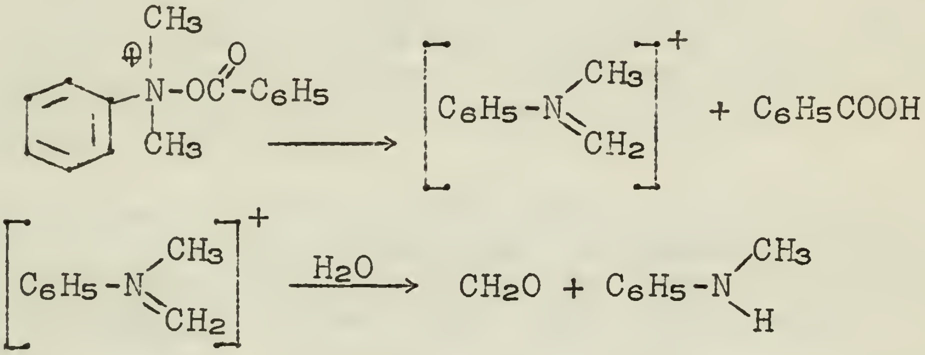
Such a mechanism accounts for acceleration by electron-donor groups on the amine and for acceleration by electron-withdrawing groups on the peroxide. However, the mechanism would be expected to show a solvent effect. The actual solvent effects observed show no correlation with such common solvent properties as dielectric constants or ionizing ability. At present no explanation of these solvent

effects is available. A similar intermediate has been proposed for the reaction between amine oxides and acetic anhydride, which has been shown to involve radicals (3,21). Both the observed products and evidence on the presence of radicals in the reaction mixture can be explained by postulating that the intermediate IX can decompose in two ways as represented in equations 1 and 2 below (4,6).

(1)



(2)



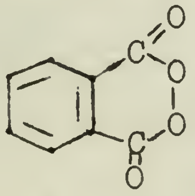
Since no nitrogen is found in the polymers formed by the reaction it is necessary to assume that the amine fragment formed in reaction (1) is incapable of initiating polymerization. Reaction (2) represents a non-radical breakdown and would account for the low efficiency of the system as an initiator of polymerization. The same products could also be produced by a radical disproportionation reaction between benzoyloxy radicals and the amminium ion radical.

Longer chain tertiary amines, such as triethylamine, yield en-amines on treatment with benzoyl peroxide. The product obtained from triethylamine is diethylvinylamine (4,6) suggested as arising from the quaternary imine intermediate.

$$(CH_3CH_2)_2\overset{+}{N}{=}CHCH_3 \xrightarrow{\text{base}} (CH_3CH_2)_2N{-}CH{=}CH_2$$

THE PHTHALOYL PEROXIDE-OLEFIN REACTION

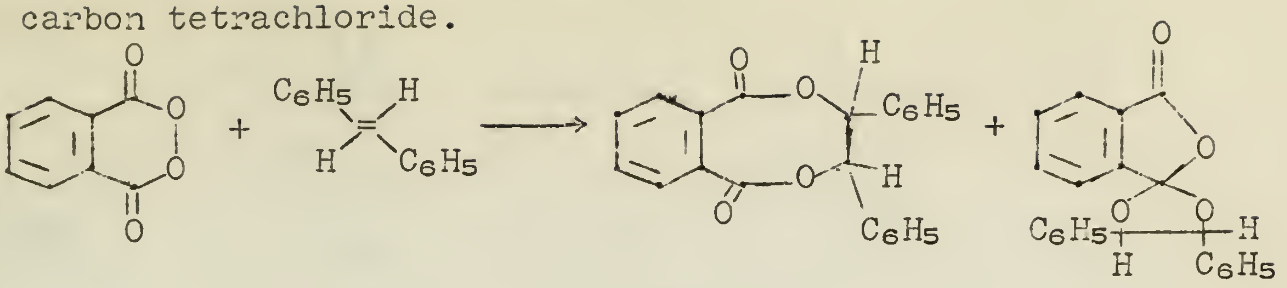
Phthaloyl peroxide X was first reported in 1953 (34) and preliminary studies on the rate of decomposition in various solvents (20,22, 23) revealed marked differences between the behavior of this peroxide and acyclic diacyl peroxides. Phthaloyl peroxide was found to be exceedingly stable in carbon tetrachloride with a half-life of 275 hours at 80° as compared with benzoyl peroxide with a half-life of 6 hours under the same conditions. In styrene, phthaloyl peroxide was found to react very rapidly (90% decomposed in 5 minutes at 75°) and the reaction was shown to follow a second order rate law. No polymerization of the styrene was found.



X

Greene has subsequently investigated the reaction of phthaloyl peroxide with olefins in considerable detail (19,20,21) and has concluded that the reaction involves nucleophilic attack by the olefin on the peroxide. Product studies were carried out with *cis* and *trans*-stilbene. With *trans*-stilbene two isomers were obtained, XI and XII, which gave analyses corresponding to the addition of one mole of peroxide to one mole of *trans*-stilbene. The reaction was carried out in re-

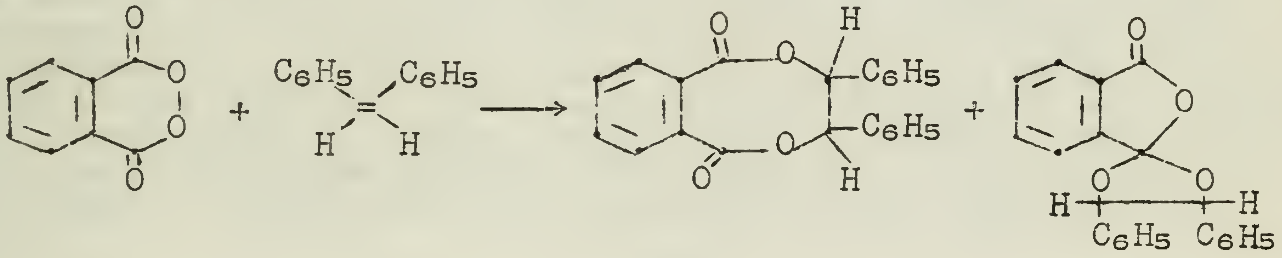
fluxing carbon tetrachloride.



XI XII

Isomer XI (phthalate) is obtained in 25% yield and isomer XII (lactone) in 75% yield. The structures were assigned on the basis of infrared and hydrolysis data. Both isomers on basic hydrolysis were found to yield phthalic acid and d,l-dihydrobenzoin. The same products were obtained using lithium aluminum hydride. Both isomers were shown to be stable under the reaction conditions.

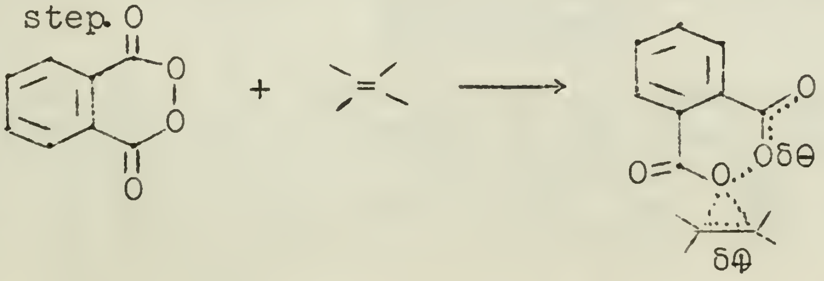
With cis-stilbene isomers XIII and XIV were obtained in 40% and 60% yields, respectively. Alkaline hydrolysis of these products in both cases was found to produce phthalic acid and meso-dihydrobenzoin. The results with cis and trans-stilbene show that the reaction is completely stereospecific.



XIII XIV

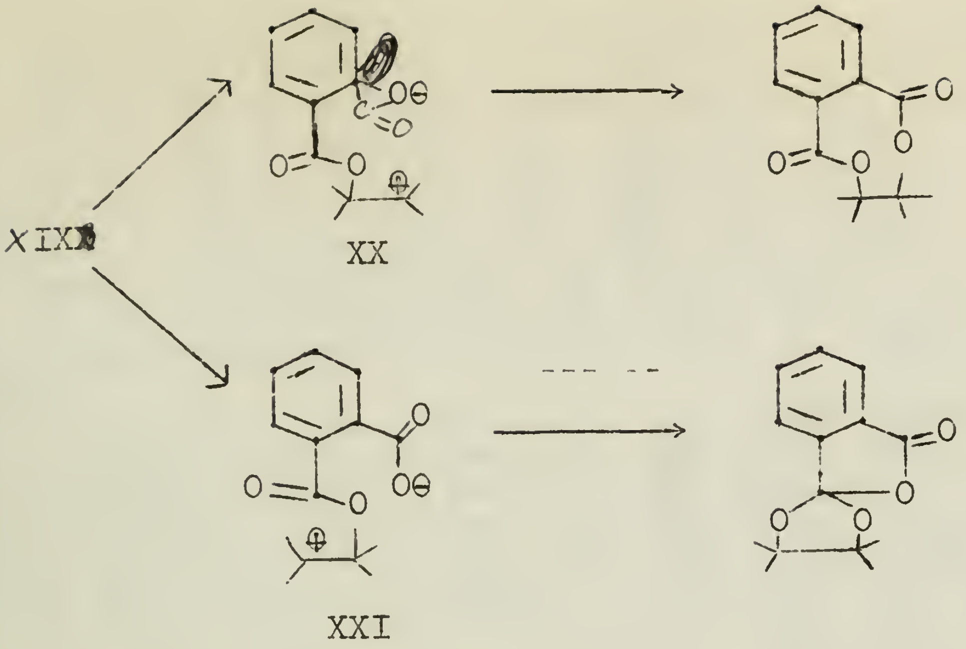
Greene has also investigated the kinetics of the reaction with a series of monosubstituted trans-stilbenes and finds a 640-fold range in rate between p-methoxy and p-nitro-trans-stilbene. The reactions were all found to follow second-order kinetics and a Hammett σρ plot was obtained by using σ^+ constants with $\rho=-1.65$. This can be taken as evidence indicating a polar mechanism although it does not rule out a radical mechanism since many radical reactions have been shown to possess some polar character.

A possible diradical intermediate was ruled out by O^{18} labeling work (22). No equilibration of oxygens occurred when phthaloyl peroxide labeled in the carbonyl groups was heated at reflux in carbon tetrachloride for 96 hours. Greene suggests the following rate-controlling step.



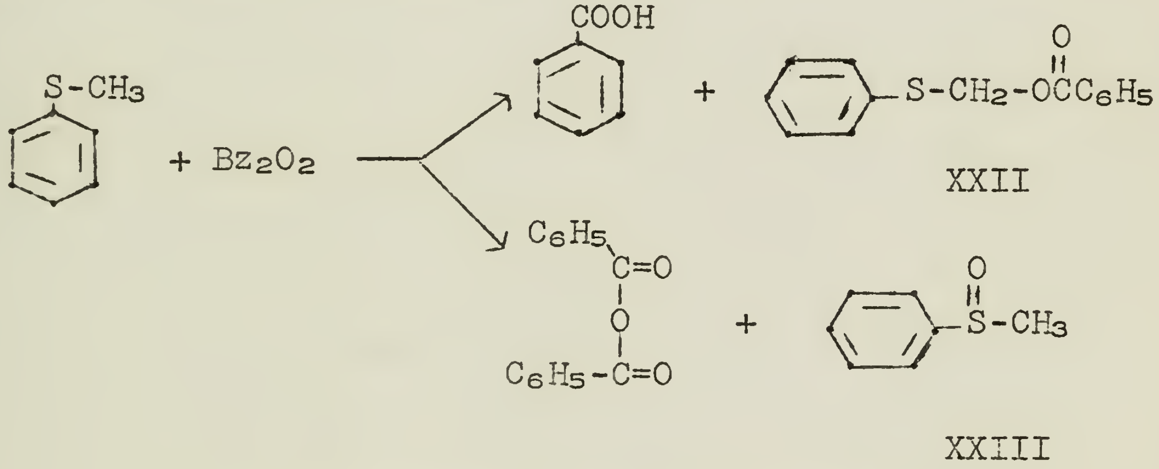
XIX

The products can be explained by partition of XIX to ion pairs XX and XXI.



PEROXIDE REACTION WITH THIOETHERS

This reaction has recently been studies by Horner (32) and appears to be another example of nucleophilic attack on benzoyl peroxide. The decomposition of peroxide was shown to follow a second-order rate law and tests for radicals (oxygen, nitric oxide and polymerizable monomers) were negative. The products from thioanisole were benzoic acid, benzoyloxymethyl phenyl sulfide (XXII), benzoic anhydride and methyl phenyl sulfoxide (XXIII). The first two of these products were formed in roughly equivalent amounts as were the last two.



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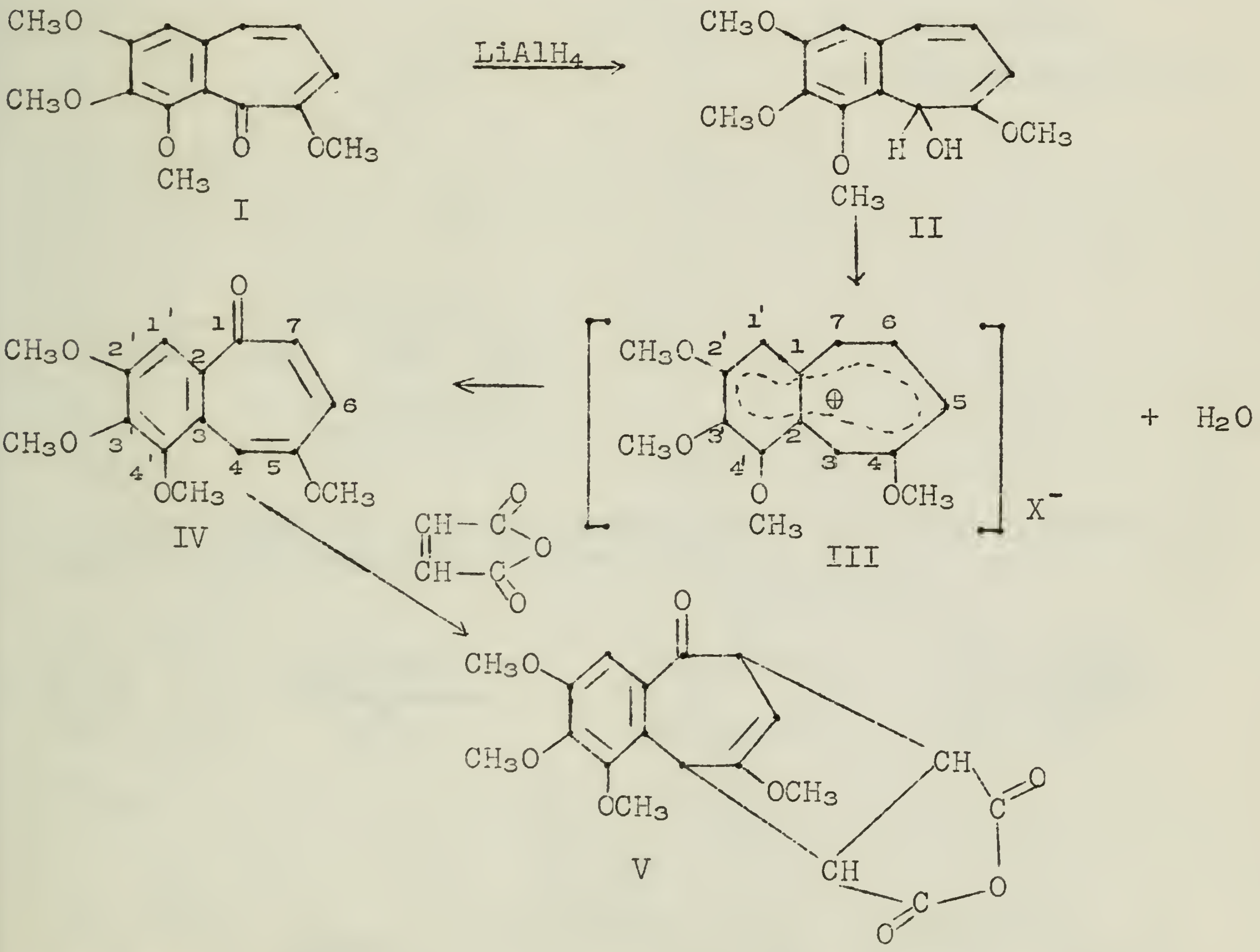
BENZOTROPYLIUM COMPOUNDS

Reported by Miss Y. Chang May 11, 1959

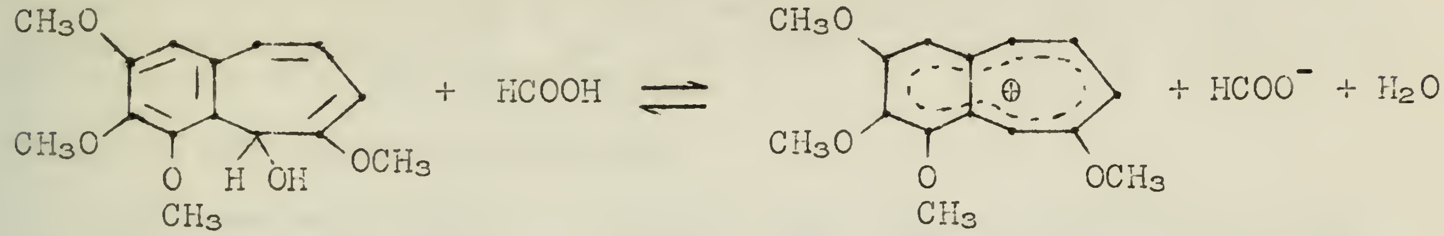
Tropylium compounds have been studied extensively in recent years (1). This seminar will be concerned with their benzologs, or benzotropylium compounds. Most of the research was done by E. Heilbronner and co-workers in Switzerland, unless specified.

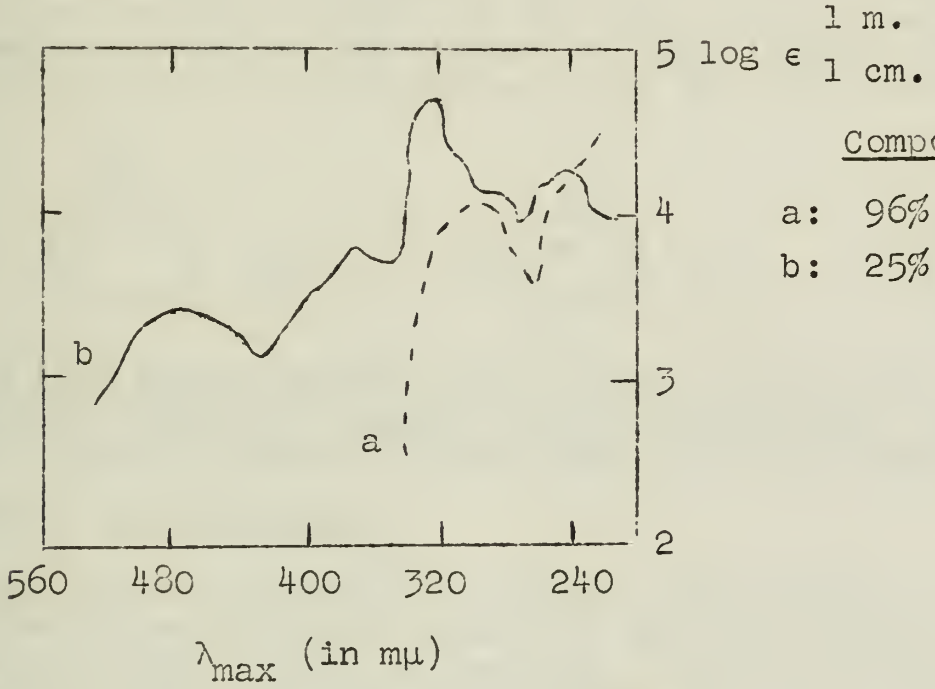
Evidence for the existence of the benzotropylium cation was given in the reduction of purpurogallin tetramethyl ether (I) (2). By using lithium aluminum hydride as the reducing agent the corresponding alcohol (II) was obtained, which gave a deep red color with dilute mineral acid. Oxidation of II with chromic trioxide in pyridine gave 2',3',4',5-tetramethoxy-2,3-benzotropone (IV), presumably with the 2',3',4',4-tetramethoxybenzotropylium cation (III) as an intermediate. The structure of IV was established by comparison with I and the formation of an adduct V with maleic anhydride. (If the carbonyl were at C-6, no adduct would be expected).



The conversion of II to III was shown by the change of spectra of II in ethanol and 25% sulfuric acid (see fig. I), which demonstrated a change in the chromophore system. The conversion was further supported by the change of conductivity of anhydrous formic

acid with and without II. In anhydrous formic acid weak base, II must exist in the form of its conjugate acid dehydrate, which produces an increase of conductivity according to:





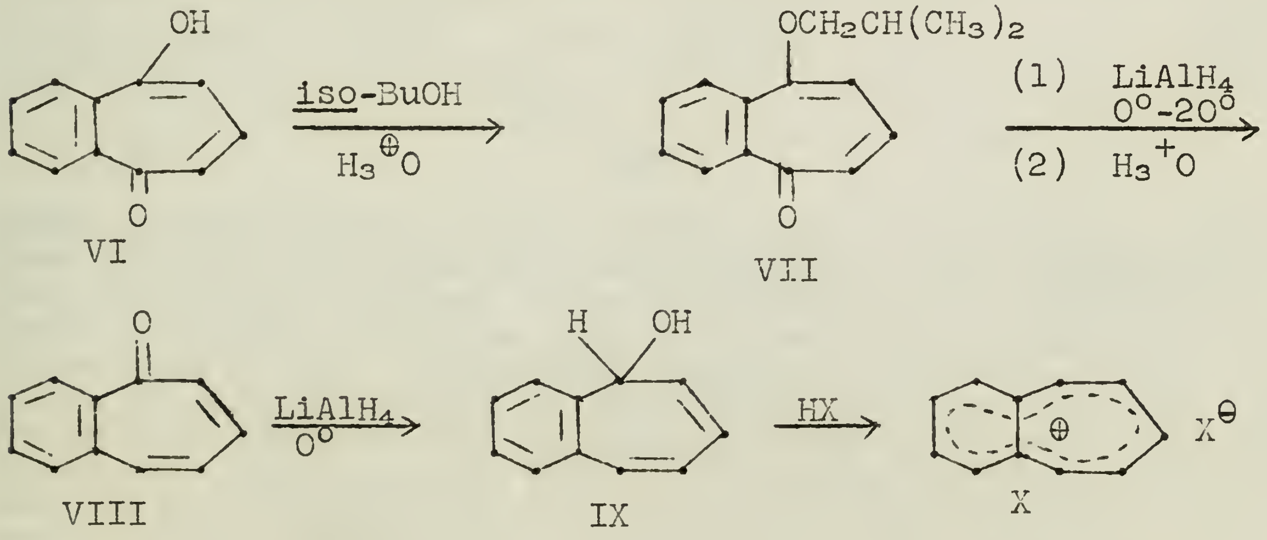
Compound II

a: 96% ethanol

b: 25% sulfuric acid

Fig. 1

The preparation of the unsubstituted benzotropylium salt was carried out in the following way (3,4):



a $X = ClO_4^-$

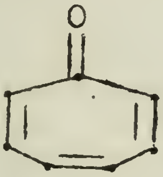
b $[PtCl_6]^{=}/2$

c HSO_4^-

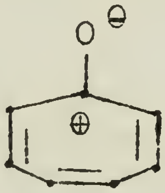
The structure of 2,3-benzotropone (VIII) was established by hydrogenation using palladium-calcium carbonate, during which two moles of hydrogen were absorbed, to 2,3-benzocycloheptanone, which was identified as its 2,4-dinitrophenylhydrazone. 2,3-Benzocycloheptadienol (IX), which had an infrared absorption band at 3350 $cm.^{-1}$, is the pseudo-base of X. For conversion to salts, the pseudo-base was treated with the acids shown.

PHYSICAL AND CHEMICAL PROPERTIES

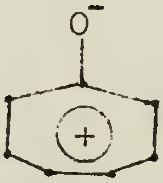
Cycloheptatrienone, or tropone, was first considered to have the structure of a conjugated ketone XIa, but its properties showed the polar resonance forms XIb and XIc to be of importance (1). Although increase in the number of fused benzene rings decreases the stability of the seven-membered ring (5), it is still reasonable to assume that benzotropones have similar properties. The following discussion will give support to this assumption, that benzotropones exist, at least to some extent as benzotropylium compounds.



XIa



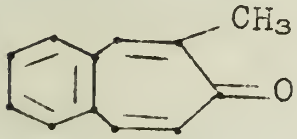
XIb



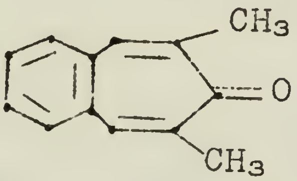
XIc

CATALYTIC HYDROGENATION

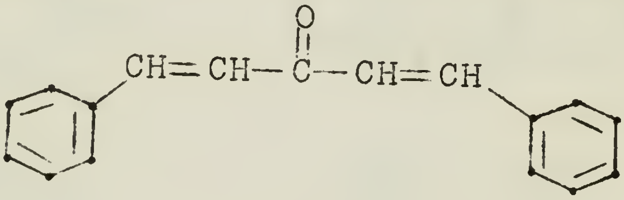
Vol´pin and Plate (6) in Russia hydrogenated 2-methyl- and 2,7-dimethyl-4,5-benzotropone (XII and XIII) using platimum black as the catalyst. Plots of rate vs. time showed a relatively low and practically constant rate of absorption of hydrogen up to the moment of saturation of first double bond, followed by a sudden rise of rate which then declined steadily. Such a phenomenon has been previously observed in the hydrogenation of acetylenic derivatives, on passing from the hydrogenation of the triple bond to that of the double bond. That this lowering of activity is not the result of conjugation in the cycloketone followed from the fact that the hydrogenation of dibenzylidene acetone (XIV) under the same condition showed a normal behavior, starting at a high initial rate which fell uniformly with the progress of the reaction. The deactivation of the hydrogenation of the first double bond in ketones XII and XIII was attributed to an effect of the carbonyl group, through an electron shift to oxygen leaving an excess positive charge on all carbon atoms of the cyclic system. This effect disappeared once the first double bond was hydrogenated.



XII



XIII



XIV

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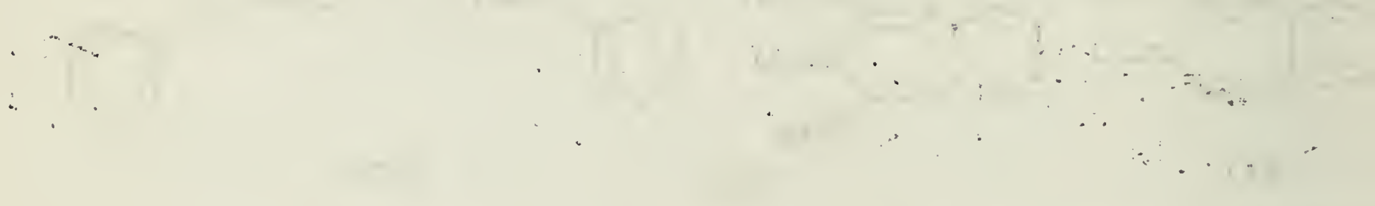

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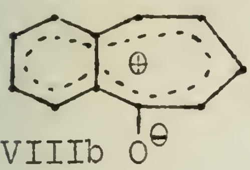
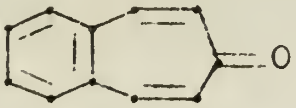
ABSORPTION SPECTRA

Infrared Absorption Spectra (4,7,8).

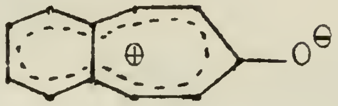
2,3-Benzotropone (VIII) and 4,5-benzotropone (XV) show rather complex structure in the range between 1700 and 1400 cm.$^{-1}$. There are peaks at 1642, 1609 and 1588 cm.$^{-1}$ for 2,3-benzotropone and 1633, 1590, 1555 for 4,5-benzotropone. The lower and stronger bands, 1588 and 1590 cm.$^{-1}$ are assigned to the carbonyl groups in VIII and XV respectively. The others are assigned to carbon-carbon double bonds. The assignment is based upon the fact that bands around 1630 cm.$^{-1}$ are unaffected by 2,7-substituents in the 4,5-benzotropones (see Table I) while the bands around 1590 are shifted. The low value for carbonyl is explained by the polar forms VIIIb and XVb in which the C-O single bond character lowers the C=O stretching frequency. As shown in table I, when the carbonyl group is forced to be out of plane, as in the case of 2,7-tetramethylene-4,5-benzotropone (XVI_4), 2,7-pentamethylene-4,5-benzotropone (XVI_5), 2,7-hexamethylene-4,5-benzotropone (XVI_6) and 2,7-di-t-butyl-4,5-benzotropone (XXI), a distinct C=O stretching band shows up.



VIIIb

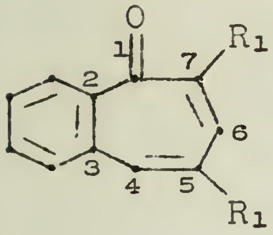


XV

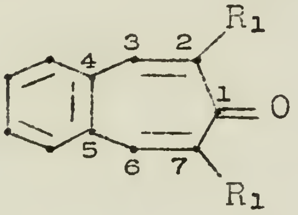


XVb

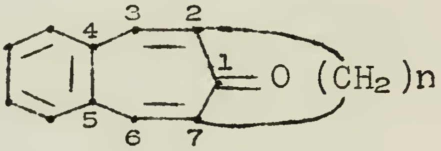
Structure Formulae for Table I.



VIII R_1 = H
XXII R_1 = CH_3
XXIII R_1 = iso-Pr



XV R_1 = H
XIII R_1 = CH_3
XVII R_1 = Et
XVIII R_1 = Pr
XIX R_1 = HX
XX R_1 = iso-Pr
XXI R_1 = tert-Bu



XVI_4 n = 4
XVI_5 n = 5
XVI_6 n = 6
XVI_7 n = 7
XVI_8 n = 8
XVI_9 n = 9
XVI_{12} n = 12
XVI_{13} n = 13

Table I Infrared Spectra (ν_{max} in cm.$^{-1}$)

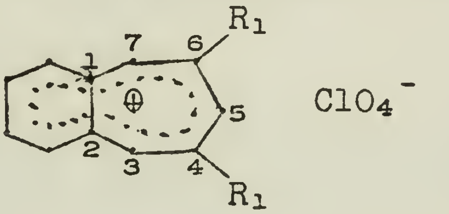
	Nujol		Chloroform		Potassium Bromide		Liquid	
	C=O	C=C	C=O	C=C	C=O	C=C	C=O	C=C
VIII	1588	1610, 1640						
XV	1590	1624	1590	1633				
XIII	1596	(1616)	1591	(1625)				
XVI_4	1724	(1617)	1727	(1623)	1717	1615		
XVI_5	1679	(1618)	1685	(1624)	1678	1622		

Table I Infrared Spectra (continued)

	C=O	C=C	C=O	C=C	C=O	C=C	C=O	C=C
XVI_6	1651	(1622)	1656		1647	1625		
XVI_7	1609	1623	1634	(1611)	1623	1610		
XVI_8	1604	1616						
XVI_9	1611	1623	1608	(1625)	1605	1620		
XVI_{12}	1590	(1615)	1593	(1615)	1590	1615		
XVI_{13}	1602	(1617)	1598	(1625)	1605	1622		
XVII							1590	1618,1555
XVIII							1593	1617,1555
XIX							1593	1616,1555
XX							1597	1627,1559
XXI					1634	1602 1557		
XXII	1580	1592 1612						
XXIII							1588	1602,1626

Ultraviolet Absorption Spectra (4,7,9).

In the series of 2,7-polymethylene-4,5-benzotropones (XVI_{4-13}). The ultraviolet spectra show dependence on "n" in both log ϵ and λ_{max}. A correlation of λ_{max} and n is plotted in Fig. 2a. In the series of 2,7-dialkyl-4,5-benzotropones (XIII, XVII to XXI), the curve is constant for the first part and then drops at 2,7-di-t-butyl-4,5-benzotropone. (see Fig. 2b) In the series of 4,6-dialkyl-benzotropylium perchlorates (XXIV), the effect of alkyl substituents on the longest wavelength band is given in Fig. 2c.



R_1=Me,Et,Pr,Hx,iso-Pr,t-Bu.

XXIV

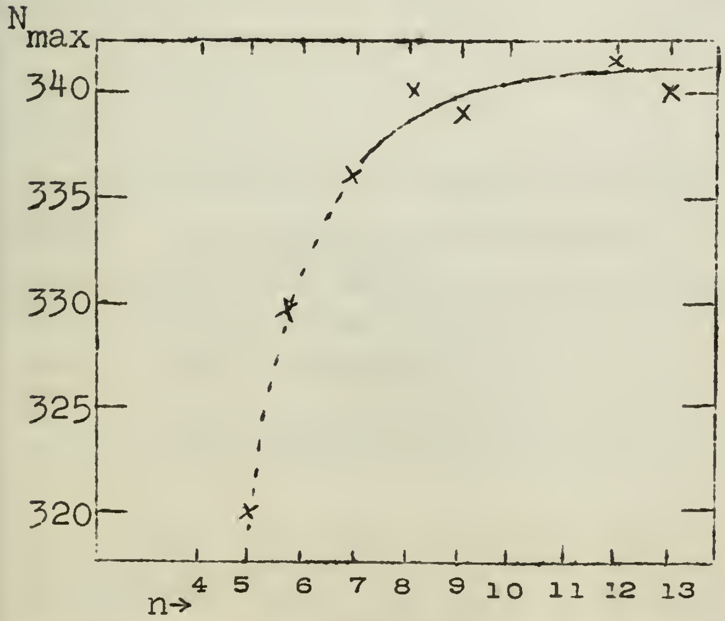


Fig. 2a

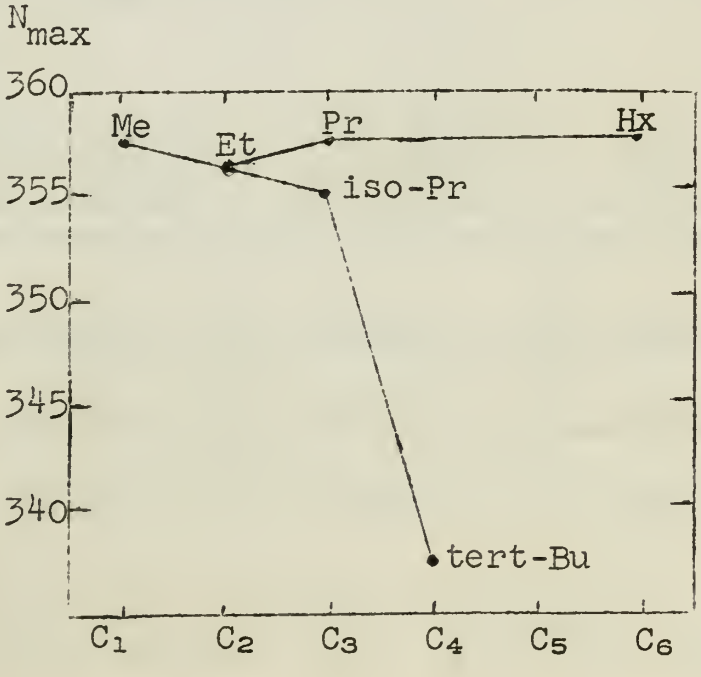


Fig. 2b

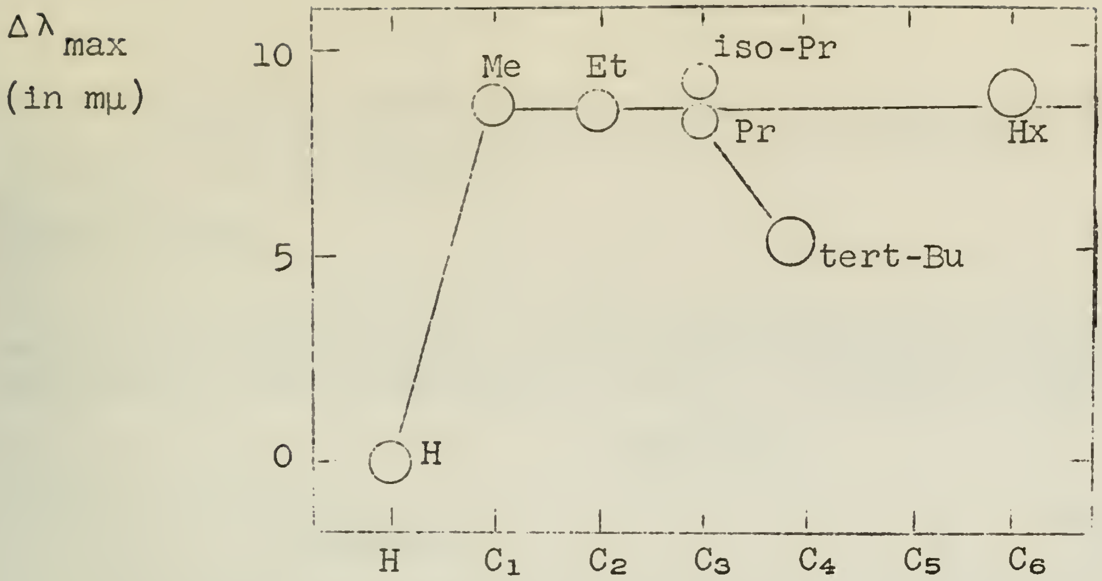


Fig. 2c

In Fig. 2a, it is shown that the long wavelength bond shifts toward higher wavelength with the increasing of n and becomes steady when n is equal to or greater than seven. This implies that a polar form exists when the carbonyl group is coplanar with the fused ring system. It is known that the sequence of increasing inductive effect which causes a bathochromic shift is Me < Et < i-Pr < t-Bu. Thus one would be surprised to see the low bathochromic shift of the t-butyl substituted compounds in Fig. 2b and 2c. This is explained by the steric hinderance of coplanarity due to the presence of t-butyl groups, or by the importance of hyperconjugation, which is in the order of Me > Et > iso-Pr > t-Bu, in the benzotropylium system.

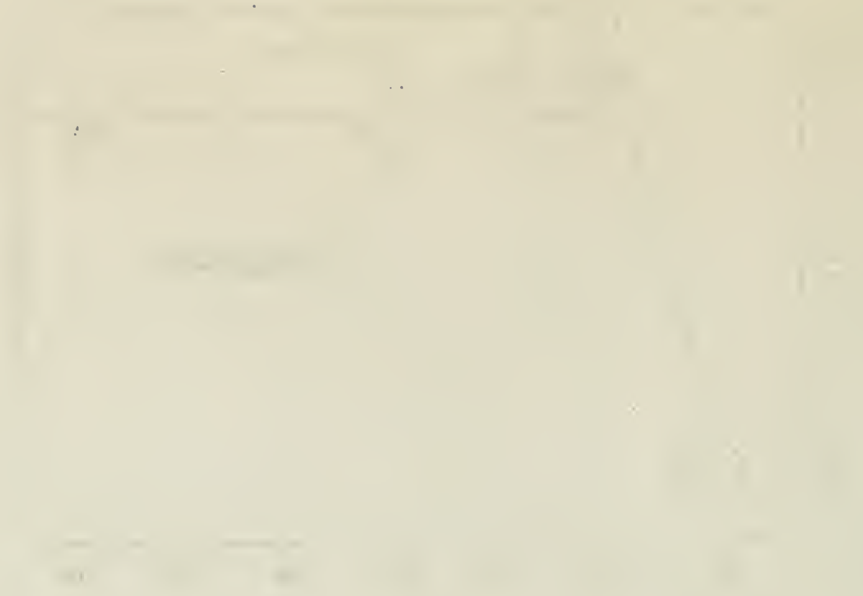
DELOCALIZATION ENERGY

Delocalization energies, or resonance energies, of 2,7-dimethyl-4,5-benzotropone (XIII), 2,7-dodecamethylene-4,5-benzotropone (XVI_{12}) and 2,7-pentamethylene-4,5-benzotropone (XVI_5) were calculated from the differences of the experimentally measured heat of formation (10) and the heat of formation calculated from the non-resonant structure using parameters given by Pitzer (11). Results of calculation and experiment are summarized in Table II.

TABLE II

		ΔH_f^o 298.16 Experimental in kcal/mol	ΔH_f^o 298.16 Calculated in kcal/mol	D.E. in kcal/mol
XIII	2,7-dimethyl-4,5-benzotropone	-2.1	+80.6	82.7
XVI_{12}	2,7-dodecamethylene-4,5-benzotropone	-41.2	+43.4	84.6
XVI_5	2,7-pentamethylene-4,5-benzotropone	+30.8	+79.5	48.7

Although the calculations are not very accurate, it is evident that XIII and XVI_{12}, in which it is possible to have a coplanar structure, have the same delocalization energies while XVI_5, which has



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an out-of-plane carbonyl group, shows a large difference. The 48.7 kcal. delocalization energy of XVI_5 was attributed to the benzene nucleus (42 kcal./mole).

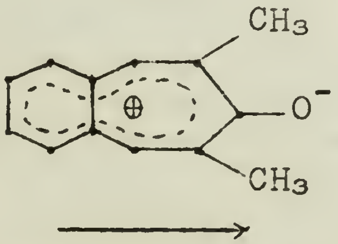
DIPOLE MOMENT

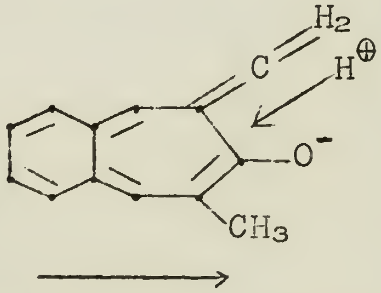
Dipole moments of acetone, benzophenone, 4,5-benzotropone, 2-methyl-4,5-benzotropone, 2,7-dialkylbenzotropones and 2,7-polymethylene-4,5-benzotropones (12,13) are given in Table III.

TABLE III

Compound	Dipole moment in Debye Units
Acetone	2.76
Benzophenone	2.93
4,5-Benzotropone	4.70
2-Methyl-4,5-benzotropone	4.25
2,7-Dimethyl-4,5-benzotropone	3.70
2,7-Dodecamethylene-4,5-benzotropone	3.49
2,7-Pentamethylene-4,5-benzotropone	3.09
2,7-Diethyl-4,5-benzotropone	3.47
2,7-Dipropyl-4,5-benzotropone	3.50
2,7-Dihexyl-4,5-benzotropone	3.43
2,7-Di-isopropyl-4,5-benzotropone	3.16
2,7-Di-tert-butyl-4,5-benzotropone	2.32

4,5-Benzotropone has a high dipole moment in comparison with the others. This can be well explained by polar character of the carbonyl group. Substitutions on the 2- or 2,7-position reduce the dipole moment markedly. By vector addition, the effect of one methyl group amounts to -0.8 D, which is much higher than the usual value -0.37 D to -0.4 D (14). This is explained by the hyperconjugation of the methyl group through the positive benzotropylium system as shown:





The difference between 2,7-dimethyl- and 2,7-dodecamethylene-4,5-benzotropone is due to the change in the number of α-hydrogens. 2,7-Diethyl-, 2,7-dipropyl, 2,7-dihexyl- and 2,7-didodecamethylene-4,5-benzotropones are constant within experimental error. Again, 2,7-pentamethylene-, 2,7-diisopropyl- and 2,7-di-*t*-butyl-4,5-benzotropones show lower moments than the unhindered ones.

MOLAR REFRACTION

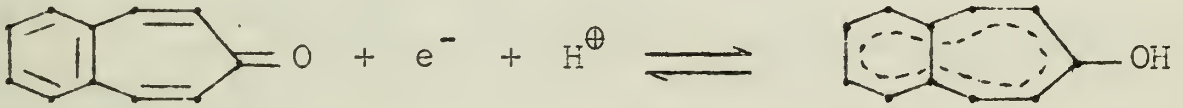
By addition of atomic polarizations (15), molar refractions based upon non-resonant structures are calculated. In comparison with experimental values (12), 2,7-pentamethylene-4,5-benzotropone has a clearly distinguished ΔMR_D value as given in Table IV.

TABLE IV

	MR_D^{20} Observed	MR_D^{20} Calculated	ΔMR_D^{20}
2,3-Benzotropone	53.0 ± 0.3	46.4	6.6 ± 0.3
4,5-Benzotropone	53.5 ± 0.6	46.4	7.1 ± 0.6
2,7-Dimethyl-4,5-benzotropone	62.5 ± 0.4	55.6	6.9 ± 0.4
2,7-Pentamethylene-4,5-benzotropone	70.0 ± 0.8	67.3	3.6 ± 0.8
2,7-Dodecamethylene-4,5-benzotropone	106.5 ± 0.8	99.8	6.7 ± 0.8

POLAROGRAPHIC REDUCTION

In the range of pH 2 to 13, half-wave potentials of polarographic reduction were measured (16) in 50% alcohol solution. The half-wave potentials of first-stage reduction $-E_{1/2}^{(1)0}$, corresponding to the following equilibrium were obtained by plotting



$E_{1/2}$ vs. pH and extrapolating to zero. They are summerized in Table V. An extremely high value was observed for 2,7-tetramethylene-4,5-benzotropone, then decreasing regularly with increase of n.

TABLE V

		$-E_{1/2}^{(1)0}$
VIII	2,3-Benzotropone	0.561
XV	4,5-Benzotropone	0.631
XIII	2,7-Dimethyl-4,5-benzotropone	0.679
XVI_4	2,7-Tetramethylene-4,5-benzotropone	1.142
XVI_5	2,7-Pentamethylene-4,5-benzotropone	1.124
XVI_6	2,7-Hexamethylene-4,5-benzotropone	0.977
XVI_7	2,7-Heptamethylene-4,5-benzotropone	0.925
XVI_8	2,7-Octamethylene-4,5-benzotropone	0.883
XVI_9	2,7-Nonamethylene-4,5-benzotropone	0.842
XVI_{12}	2,7-Dodecamethylene-4,5-benzotropone	0.828
XVI_{13}	2,7-Tridecamethylene-4,5-benzotropone	0.793

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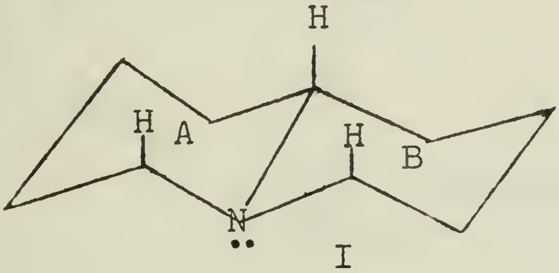
CONFIGURATION, CONSTITUTION AND CONFORMATION IN THE QUINOLIZIDINE ALKALOID SERIES

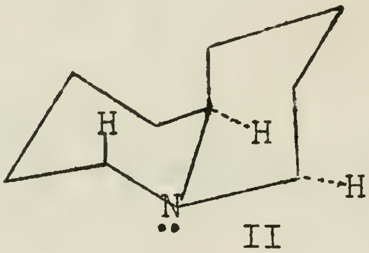
Reported by C. K. Steinhardt May 18, 1959

Lupin or quinolizidine alkaloids are found in a wide variety of plants and small trees, and because as a group these alkaloids are toxic, they sometimes render the plants unfit for use as fodder (1).

The quinolizidine ring system (I) is the unit common to this group of alkaloids. During work on the synthesis of some sparteine derivatives (2) Bohlmann noticed a correlation of the type of quinolizidine ring fusion to a group of bands in the C-H stretching region of the infrared spectra of these compounds. Specifically he found that a group of bands appear in the range 2800-2700 cm.$^{-1}$ in bases which contain a *trans*-quinolizidine ring without a lactam group. These bands are absent in *cis*-fused quinolizidine rings (II). In order to determine the usefulness of these bands for determination of configuration, Bohlmann and his coworkers (3) measured the spectra of a number of sparteine derivatives, the relative stereochemical configurations of which had been provisionally assigned by Marion and Leonard (4) in 1951 on the basis of a study of models and the known stereospecific course of hydrogenation (5) in this series. An X-ray diffraction analysis (6) of α-isosparteine monohydrate confirmed the original assignment of Leonard and Marion, thus providing Bohlmann with some known models on which to test the worth of these bands for determination of configuration.



I



II

Further work by Bohlmann (3) demonstrated that these bands do not appear if an N-oxide is present or if there is a double bond at the ring fusion. Thus the bands arise only if at least two C-H bonds (or a C-H and a C-D bond) on carbon atoms adjacent to the amino nitrogen are *trans* to the isolated electron pair on nitrogen, which is the case only in the *trans* quinolizidine conformation. In *cis*-fused quinolizidine rings only one α-C-H bond is *trans* to the electron pair on nitrogen. The presence of some *cis*-conformer together with the *trans*-conformer would not be detectable in the quinolizidine case. In the lactams the isolated electron pair is no longer available for interaction with the *trans* C-H bonds because of resonance delocalization. Similar considerations operate in the case of a double bond at the ring fusion so that the bands disappear.

From these considerations Bohlmann has concluded that these infrared maxima result from an interaction between neighboring *trans* C-H bonds and the isolated electron pair on nitrogen, and that this

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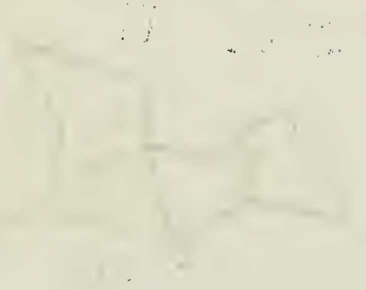

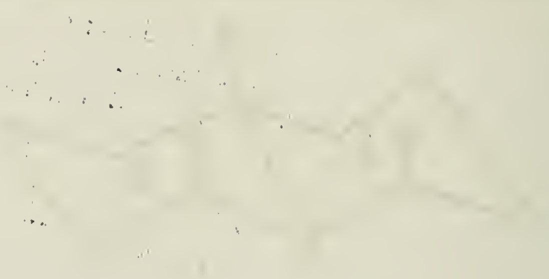

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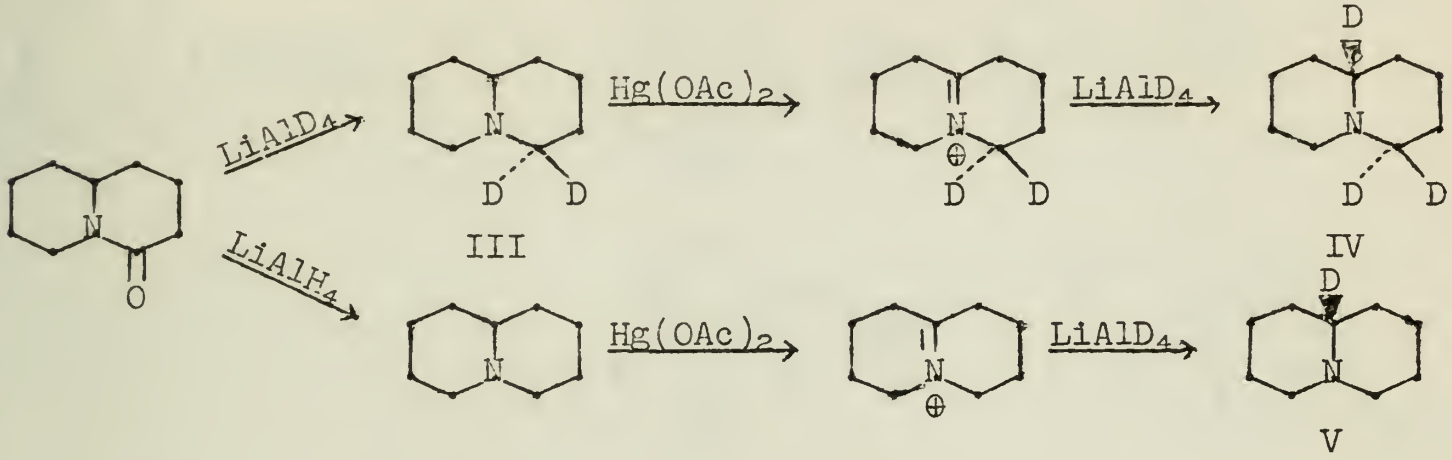
interaction is due to a "resonance" of the electron pair on nitrogen and the σ orbitals of the C-H bond which lie in a plane.

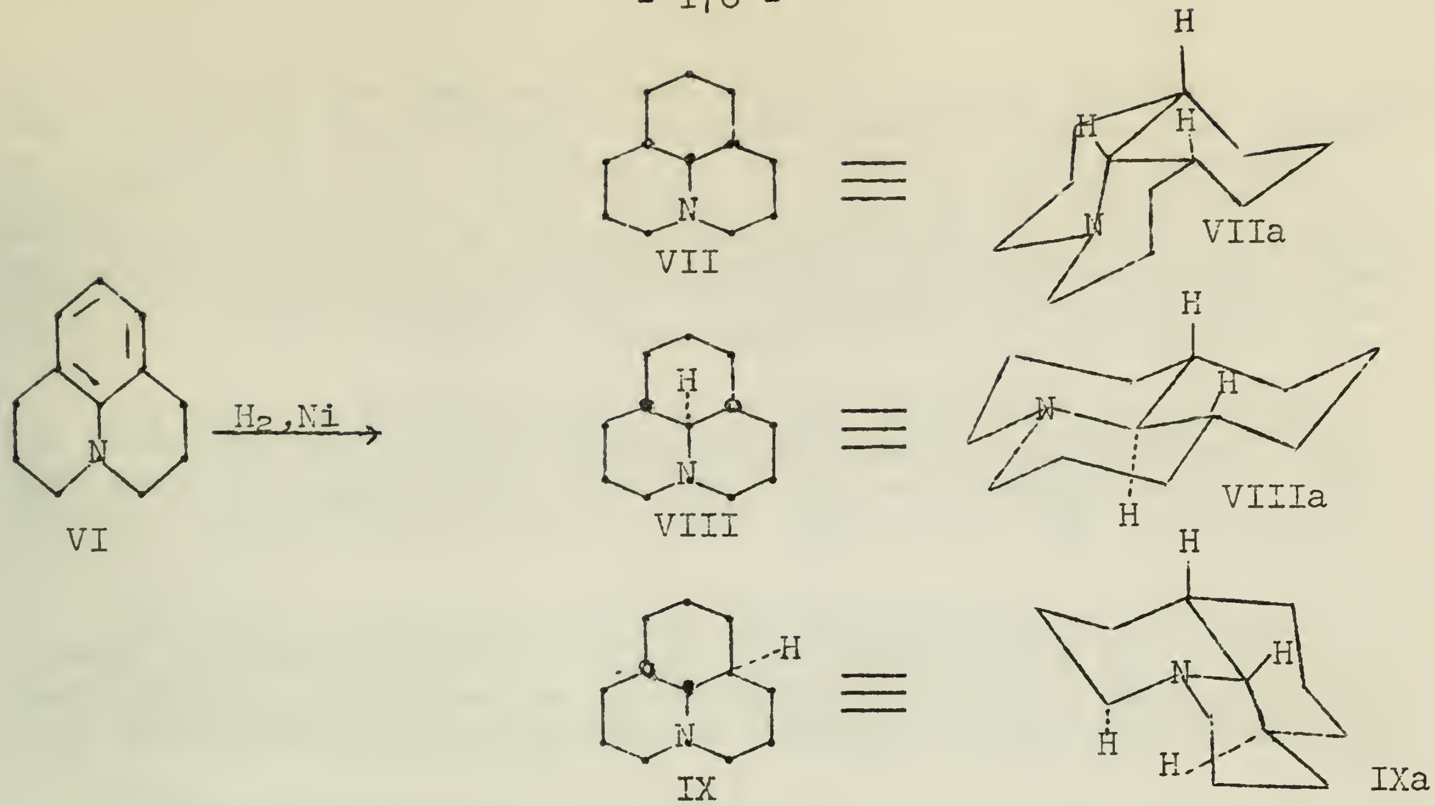
In trying to clear up the question of whether these bands are genuine C-H vibrations or overtones or combination frequencies, a series of deuterated bases were prepared from quinolizidone, and another series from sparteine derivatives. The synthesis of the deuterated quinolizidines is shown below.



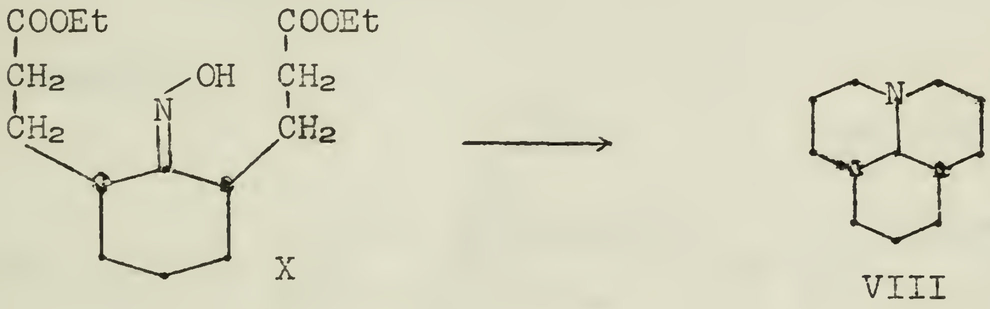
The spectra of III - V showed that in addition to the normal C-D absorption, 2100-2200 cm.$^{-1}$, a new band at about 2000 cm.$^{-1}$ appears, which Bohlmann assigned to the C-D interaction with the isolated electron pair on nitrogen. This band disappears upon the formation of the amine oxide. Leonard and Sauers (7) had previously prepared V by another method and reported that five distinct bands were noted in the 2090-1948 cm.$^{-1}$ region; these have not yet been accounted for theoretically. In addition to the appearance of the new maxima, the bands between 2800 and 2700 cm.$^{-1}$ decrease in intensity because of the substitution of C-D bonds for C-H bonds. This decrease in intensity was even noticeable in the case of 10-methylquinolizidine. It is interesting to note that the N-oxide of IV has no bands either in the 2800-2700 cm.$^{-1}$ region or in the 2000 cm.$^{-1}$ region. Entirely analogous effects were observed in the deuterated sparteines.

Dr. Corey has suggested that while Bohlmann's interpretation may be valid for the above cases, often bulk and steric effects can be very important in such a system and that the bands in the 2800-2700 cm.$^{-1}$ region might be very sensitive to such effects (8).

In the course of the investigation of the configuration of matrine, a naturally occurring quinolizidine alkaloid, the three isomers of hexahydrojulolidine, a base which contains part of the basic structure of matrine, were prepared as model compounds (9).



A mixture of the three theoretically possible stereoisomers of hexahydrojulolidine is obtained upon catalytic hydrogenation of julolidine (VI) over Raney nickel. Protiva and Prelog (10) had previously separated two isomers from the reduction mixture, but had not assigned the configurations. Leonard and Middleton (11) in 1952 synthesized an isomer which had a picrate m.p. of 186° (thus similar to one of Protiva and Prelog's isomers) by a different method involving the reductive cyclization of the oxime of diethyl cyclohexanone-2,6-di-β-propionate (X) over copper chromite at 265° and 350 atm. In the light of recent work which has reversed most of the



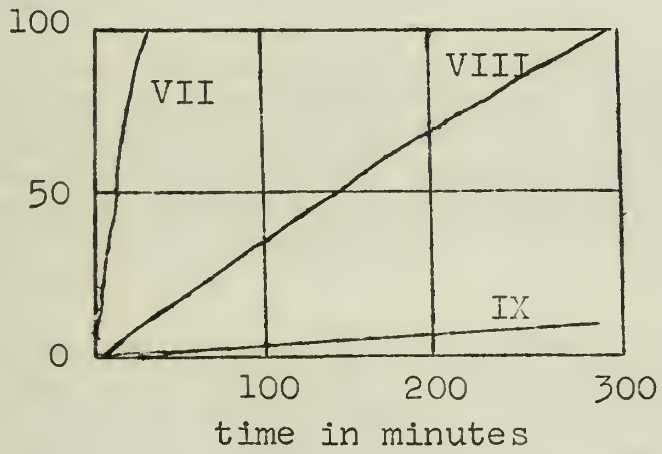
original Cornubert assignments in the 2,6-dialkylcyclohexanone series and has shown the greater stability in general of the cis-1,3-equatorial positions for large groups, we would expect the ester groups to be diequatorial and thus ring closure would give the most stable isomer VIII. The work of Bohlmann (9) establishes the true relative configurations of VII, VIII, and IX.

The mixture of isomers obtained by catalytic hydrogenation of julolidine was separated by chromatography on alumina and the expected three hexahydrojulolidines were obtained whose picrates melted at 225°, 186°, and 182°. The melting points are listed in the

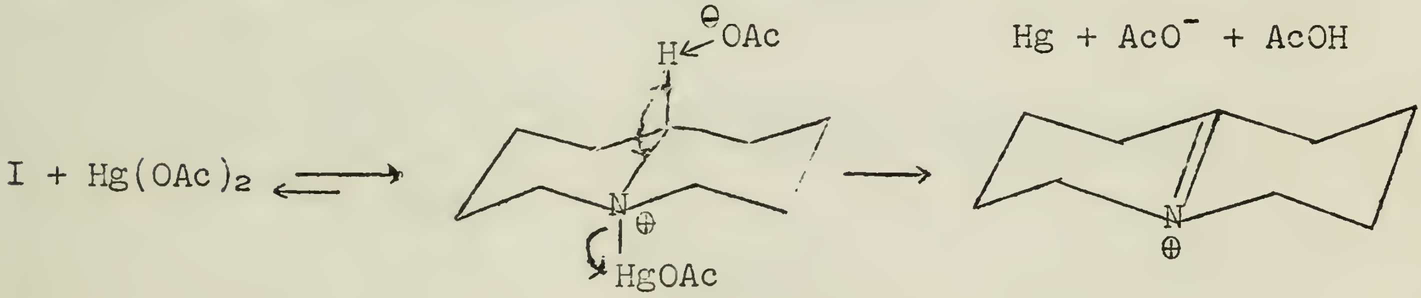
order in which the compounds were eluted from the column. The infrared spectra of the first two compounds eluted indicate the presence of trans-fused rings (assuming all chair forms) while the third compound (picrate m.p. 182°) shows no bands in the 2800-2700 cm.$^{-1}$ region and thus must be the cis-fused compound IX. This assignment is confirmed by the resolution of IX into its enantiomorphic forms with 6,6'-dinitrodiphenic acid. The resolution also provides more evidence for the utility of these bands in structure determination.

The base whose picrate melts at 186° and which is obtained by the reductive cyclization described by Leonard and Middleton (11) must have the trans-trans structure VIII as discussed above. Thus the base whose picrate melts at 225° has the all cis configuration VII.

The rate of mercuric acetate dehydrogenation of the three isomers was next determined since this reaction was important for configuration determination in the matrine series. The mechanism of this dehydrogenation was assumed by Leonard, Miller and Thomas (12) to be as follows:



Dehydrogenation of VII, VIII, and IX with mercuric acetate.



If it is assumed that the tertiary hydrogen must be trans to the isolated electron pair on nitrogen, then IX, in which the tertiary hydrogen is cis, should react substantially slower as indeed it does. Complex formation does not seem to be a rate limiting step. Bohlmann has suggested that IX does not react at all from conformation IXa but instead from the very unfavorable double boat conformation formed by inversion of configuration of the nitrogen atom. Pyrrolizidine, which probably exists only in the cis-fused form (since the form in which the tertiary hydrogen is trans to the

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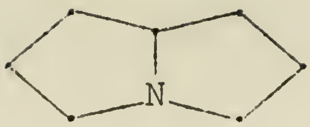


Pyrrolizidine

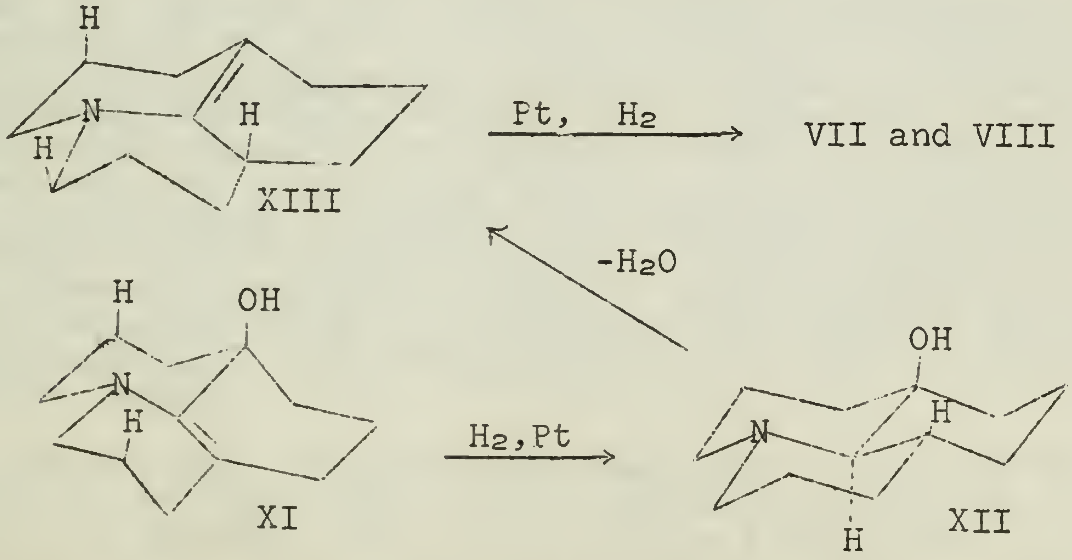
electron pair on nitrogen is at least seven kcal. higher in energy), was recovered unchanged from a reaction carried out under conditions similar to the dehydrogenation of the hexahydrojulolidine, even after a very long time.

An alternative explanation is that the reaction took place at the secondary hydrogen which is trans to the electron pair on nitrogen. This reaction would, of course, give an isomeric dehydro base, a possibility since no product analysis was performed.

Compound VII reacts about five times as fast as VIII. This rate difference may be rationalized by the fact that VIII has a configuration more stable than VII and thus there is a greater driving force for the reaction of VII. The behavior is quite analogous to the dehydrogenation of cyclic alcohols to ketones, in which it is the non-classical strain in the initial base which is significant for the reaction velocity (13).

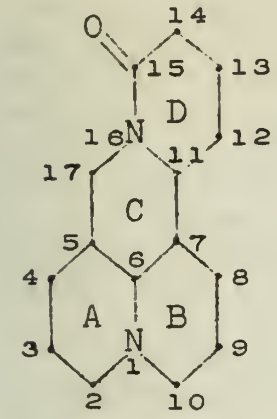
In the dehydrogenation of VIII a secondary reaction occurs which gives rise to the hydroxydehydro compound XI, and in fact this secondary reaction proceeds very rapidly since even after 50% dehydrogenation only the hydroxydehydro compound XI was isolated. The product showed no characteristic bands in the 2800-2700 cm.$^{-1}$ region, thus confirming the fact that the double bond was at the ring fusion.

Compound XI was hydrogenated catalytically to give XII. To prove the configuration of XII it was dehydrated to give XIII, the normal dehydro base obtained by mercuric acetate dehydrogenation of VII. Catalytic hydrogenation of the perchlorate of XI also yielded XII. By contrast, catalytic hydrogenation of XIII or its perchlorate salt gives an equal mixture of VII and VIII.

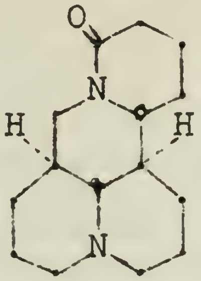


With the background provided by the work of julolidine, Bohlmann and his coworkers proceeded to the problem of determining the configuration of matrine (14). The gross structure of matrine had already been established as indicated by the formula below (15, 16,17,18). For a base of this structure there are eight possible racemates. Of these eight possible racemates four can immediately

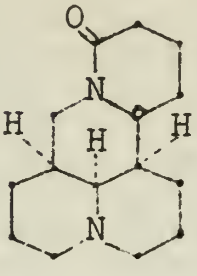
be eliminated as possibilities for dl-matrine, since matrine exhibits the characteristic trans bands at 2800-2700 cm.$^{-1}$ the possibilities XIV, XV, XVI, and XVII remain. Only one of the enantiomorphic forms is shown.



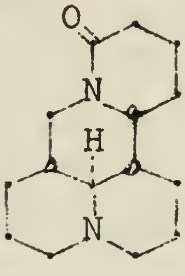
matrine



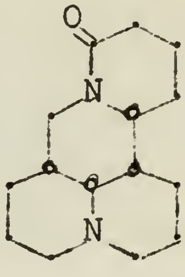
XIV



XV



XVI



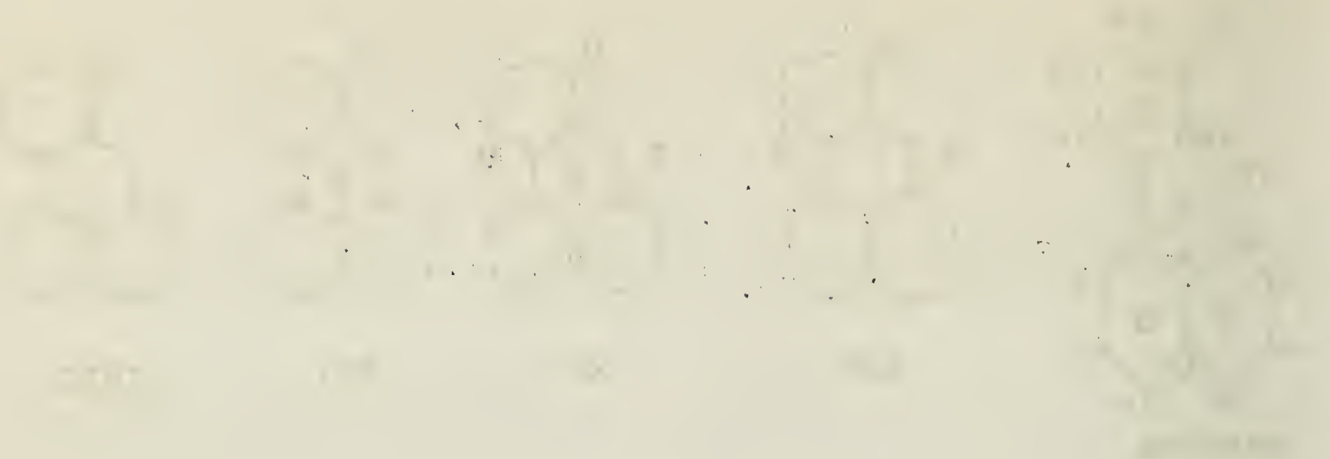
XVII

These four configurations can be subdivided into two pairs, XIV and XVI in which C is fused trans to A and B, and XV and XVII in which a cis fusion is present. In XIV and XV a trans fusion of C with D is assumed to be the most stable configuration, while in XVI and XVII a cis fusion of C and D must be more stable since a trans fusion is possible only with boat forms. Throughout this argument the existence of only chair forms is assumed by Bohlmann. Thus, XIV-XVII are respectively trans-trans, cis-trans, trans-cis, and cis-cis in the fusion of A and B to C and C to D.

Since matrine is converted to allomatrine, another alkaloid of the same constitution as matrine, upon heating with copper chromite at 230-250° under a hydrogen atmosphere (15), it must be the most stable isomer, namely XIV. Allomatridine (desoxyallomatrine) was obtained by the synthesis of Schöpf (18) which would probably lead to the most stable isomer.

In order to obtain additional support for the above assumptions, Bohlmann (14) carried out a mercuric acetate dehydrogenation on both matrine and allomatrine. From experience with dehydrogenation of the isomers of hexahydrojulolidine it would be expected that matrine would dehydrogenate faster than allomatrine, since it is the less stable isomer. The experiment bears out this prediction, since matrine reacts about six times as fast as allomatrine. A similar relationship is observed with matridine and allomatridine. The mercuric acetate dehydrogenation of matrine yields in addition to the expected dehydro base (XVIII) a hydroxydehydro base (XIX). From the dehydrogenation of allomatrine only XIX was isolated--behavior analogous to the dehydrogenation of VIII in the hexahydrojulolidine series.

Since the same hydroxydehydro base XIX is obtained from matrine and allomatrine, they must be distinguished only by the configurations of the hydrogen atoms on the carbon atoms joined by the double bond, which--as will be shown later--are C-6 and C-7. Thus, the fusion of rings A and B to C is the only factor which distinguishes allomatrine from matrine. We then know that allomatrine and matrine are either XIV and XV or else they are XVI and XVII, respectively. These pairs are distinguishable by the ring fusion of C to D, since in the first pair it is trans and in the second cis, as previously



mentioned. Reduction of the lactam group in the dehydro base XVIII yields dehydromatridane XXVII. Bands in the 2800-2700 cm^{-1} region will not arise from rings A and B, because the double bond occurs at this ring fusion. Therefore, the presence or absence of the bands will indicate the type of fusion between rings C and D. Since XXVII exhibits these bands, rings C and D are trans fused and we may now say that allomatrine is XIV and matrine is XV. Further evidence that XV is the structure of matrine is obtained by the reduction of dehydromatrine perchlorate (XVIII perchlorate) with sodium borohydride to give only matrine. The 11, 17 diaxial hydrogens of the C ring impede the approach of the BH_4^- from attack on the "upper" side of the molecule. Attack from the less hindered side leads to matrine. Dehydromatrine XVIII upon catalytic hydrogenation also leads only to matrine and the same argument applies.

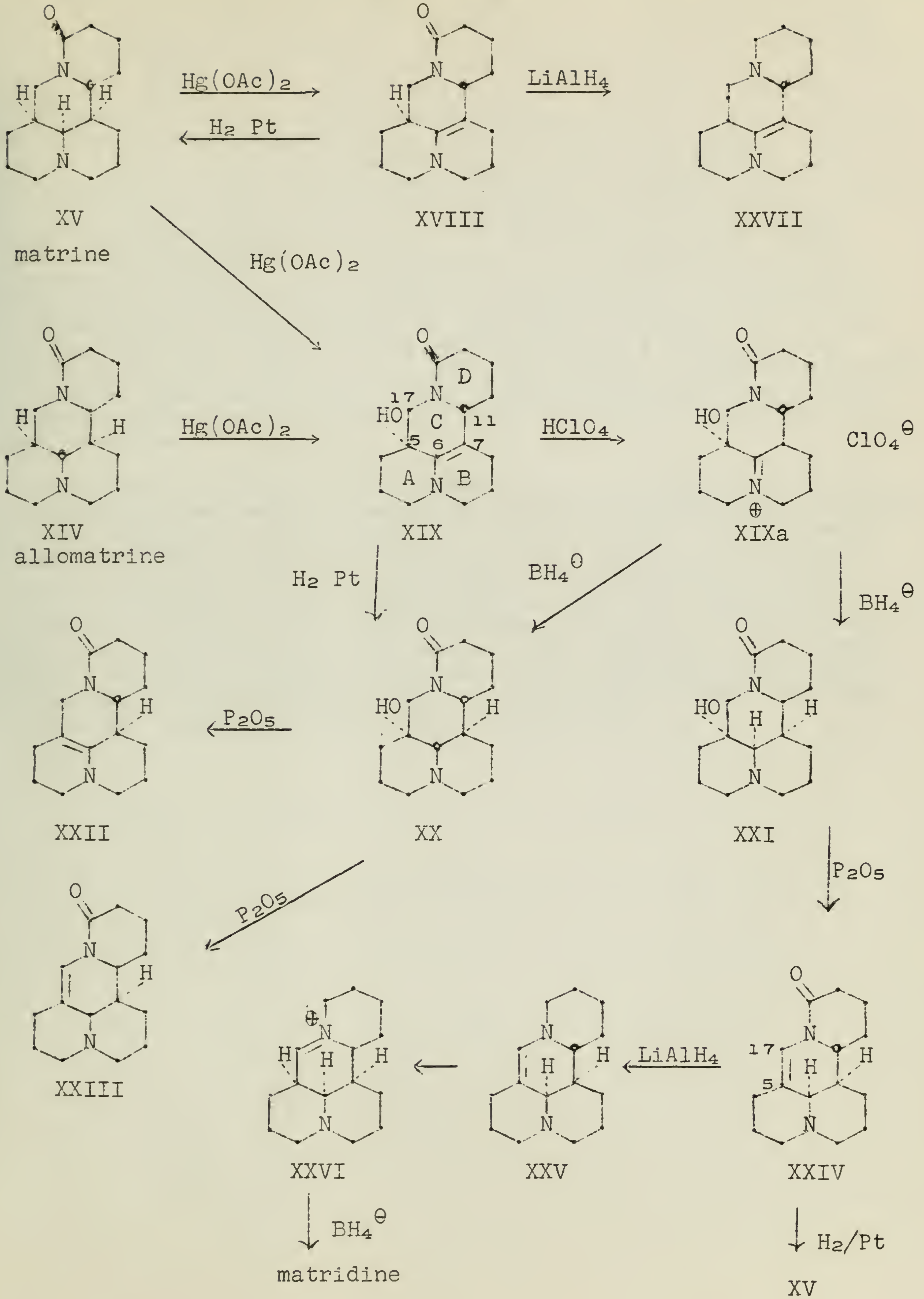
The following experimental work was undertaken by Bohlmann (14) in order to establish the position of the double bonds in XVIII and XIX.

The perchlorate (XIXa) of XIX was formed and reduced with sodium borohydride to form 5-hydroxyallomatrine (XX) in good yield plus a small quantity of 5-hydroxymatrine (XXI). The alcohols were chromatographically separated, and infrared spectra indicate that both compounds have trans fused A and B rings. Catalytic hydrogenation of XIX in methanol also gives a chromatographically separable mixture of XX, XXI, and a third compound whose A-B ring fusion is cis according to the infrared spectrum. Dehydration of XX over phosphorus pentoxide yields two dehydromatrines which were separated by chromatography. The first compound eluted is XXII since no trans bands appeared in the infrared. The second compound is then doubtlessly XXIII. The formation of two dehydromatrines is easy to reconcile with configuration XX since there are two hydrogens trans to the OH group.

Since XXII is different from the dehydromatrine obtained from matrine (XVIII), XVIII must have the double bond in the same position as XIX. Bohlmann made the assignment of the double bond in XVIII and XIX to either the 6-5 or 6-7 position on the basis of the following considerations. Compound XXI was dehydrated with phosphorus pentoxide to give XXIV. If we assume that this hydrogenation can only be a cis addition, then XXIV must have the double bond in the 5-17 position rather than the 7-11 position. It must be pointed out, however, that "trans-addition" or at least rearrangement during hydrogenation is not impossible and that indeed in the julolidine series the net result of catalytic reduction of XI is "trans-addition". The appearance of VIII on reduction of XIII is also unexpected. Bohlmann offers additional evidence, however, for this assignment. Reduction of the carbonyl group in XXIV with lithium aluminum hydride followed by conversion to the perchlorate and borohydride reduction gives only matridine. This is much easier to rationalize with the double bond's being in the 5-17 position since then the hydrogen at C-11 is not disturbed.

Once the double bond is established to be in the 5-17 position, the hydroxyl of XXI is on C-5, the double bonds in XXIII and XIX are in the 6-7 position, and the rest of the positions are as shown in Chart 1.

Chart I


XV
matrine
Hg(OAc)₂
H₂ Pt
XVIII
LiAlH₄
XXVII
Hg(OAc)₂
XIV
allomatrine
Hg(OAc)₂
XIX
A
B
C
D
5
6
7
11
17
HClO₄
XIXa
ClO₄⊖
H₂ Pt
BH₄⊖
BH₄⊖
XXII
P₂O₅
XX
XXI
P₂O₅
XXIII
P₂O₅
XXVI
XXV
LiAlH₄
XXIV
BH₄⊖
matridine
H₂/Pt
XV

Shortly before Bohlmann published the work described above, Tsuda and Mishima (19) published a note in which the configurations of matrine and allomatrine were assigned on the following grounds. The main assumption involved in their assignment is that the C and D rings are trans-fused. The evidence they advanced to support this assumption, namely that boiling alkali does not convert matrinic or allomatrinic acid into the corresponding isomer, is not sufficient (20). The work of Bohlmann puts this assumption on sounder ground, however. The following considerations by Tsuda and Mishima led to the assignment. (A.) Cyanogen bromide does not attack matrine (therefore N-1 is shielded), whereas it attacks allomatrine forming two bromoallomatrine cyanamides, m.p. 126° and 166°; (B.) matridine forms a monomethiodide, in which only N-16 is quaternized, while allomatridine forms a dimethiodide; (C.) the velocity of hydrogen liberation in palladium-on-asbestos dehydrogenation of matrine is four times that of allomatrine, of matridine is twice that of allomatridine, therefore the matrine series possesses more cis C-H bonds than the allo series; (D.) the allo series is thermodynamically more stable than the matrine series since as was mentioned earlier, matrine is converted to allomatrine upon heating with hydrogen and copper chromite.

Measurement of the dipole moments (21) of matridine and allomatridine and some related compounds has provided additional evidence for the assignments of configuration in this series. For example allomatridine has a moment nearly twice as great as quinolizidine or hexahydrojulolidine, while matridine has a moment only about 1.15 times as great. This result fits in well with the assigned structures of allomatridine and matridine since to a first approximation the moments of the compounds are the resultant of the group moments located at the $N-C_3$ portions of the molecule, and in XIV the two group moments are parallel to each other whereas they make a tetrahedral angle with each other in matridine.

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STUDIES IN THE D-HOMOSTEROIDS

Reported by S. J. Fusco May 21, 1959

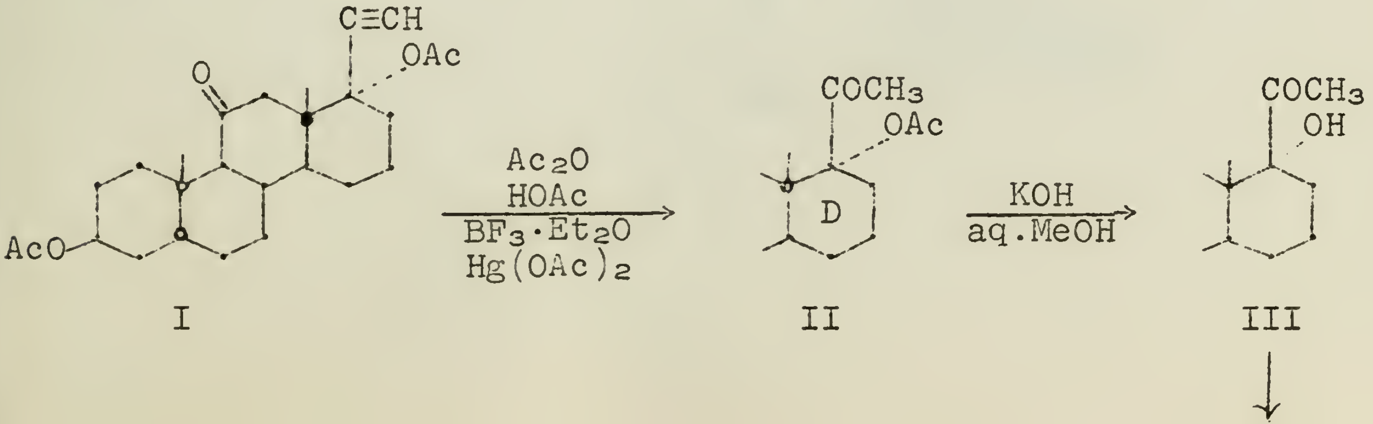
INTRODUCTION

The D-homosteroids, in which the normal five-membered D-ring of steroids is replaced by a six-membered ring, have been the subject of a considerable amount of recent research. The reasons for the great interest in these homologues are manifold, but there seem to be three fields in which much of the interest has been concentrated: the partial synthesis of D-ring homologues of the biologically active steroids, studies of reaction mechanisms, and the total synthesis of steroids. Synthetic homologues of biologically active compounds have always been of great importance to pharmacologists and biochemists for their studies of the relation of activity to structure. Examination of the stereoelectronic requirements of many reactions is simplified, to a large extent, by the rigid structure of the steroid nucleus. The total synthesis of important steroids may be made possible *via* the D-homo derivatives, since these are easier to prepare, and are readily converted to the normal steroids. In this report, examples of significant advances in each of these fields of interest will be examined.

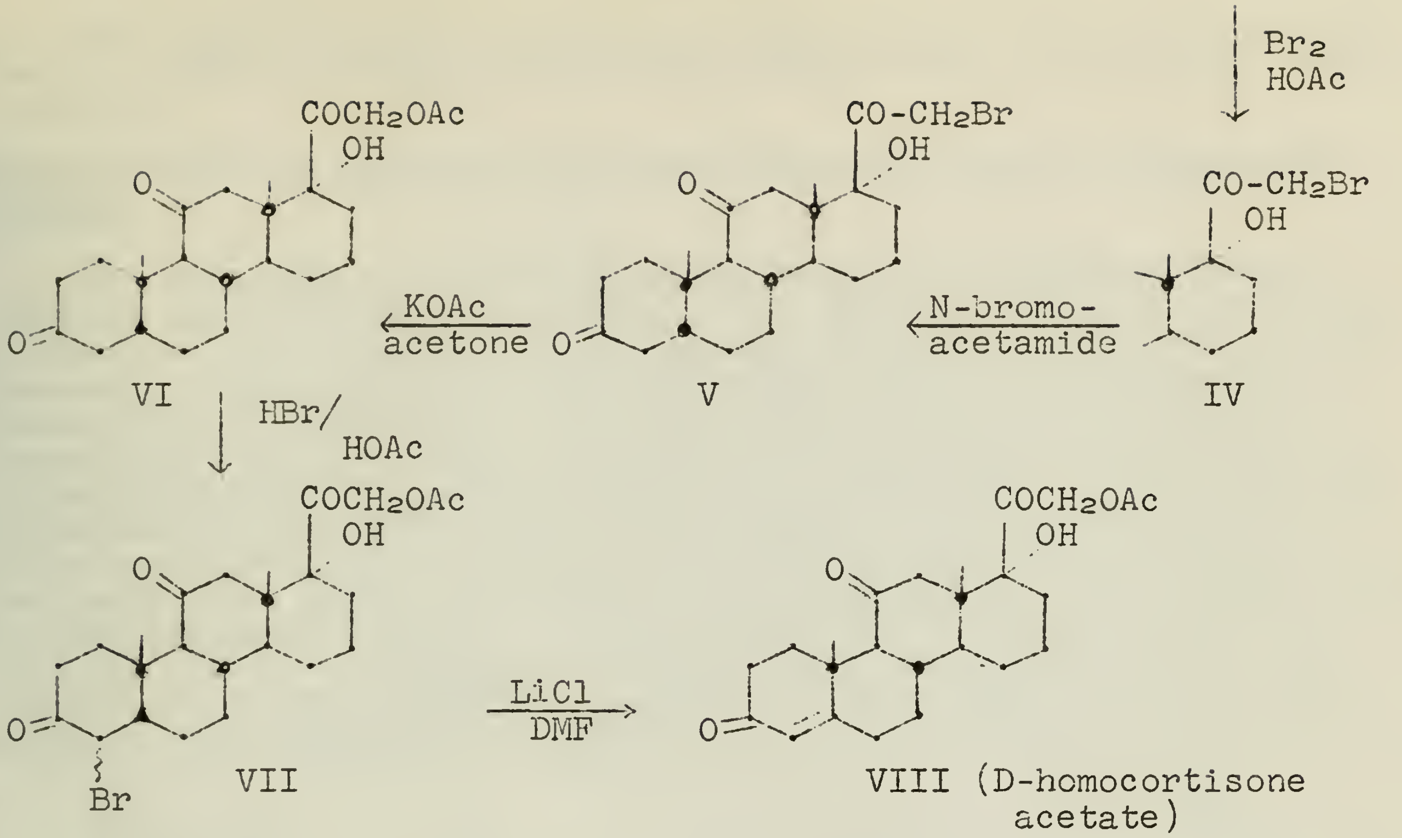
HOMOLOGUE SYNTHESES

Since the accidental discovery of the D-homosteroids by Miescher and Kagi in 1939 (1), biochemists have been interested in the physiological activity of these steroid homologues. Concentrated efforts have led to the synthesis of at least two biologically active D-homosteroids, D-homocortisone acetate (2,3) and 17aα-methyl-D-homotesterone (4).

The approach to the synthesis of D-homocortisone acetate involved the addition of an ethynyl group to the 17a-ketone of D-homoetiocholane-3α-ol-11,17a-dione (2). In the normal steroids, this reaction gives only a 0.3% yield of the desired isomer (the 17α-hydroxy compound). Considerations of models led Clinton and his coworkers (2) to the prediction that steric hindrance on the back side of the D-homo derivative would be increased due to the axial hydrogens at C-12,14, and 16. The mixture obtained should be somewhat enriched in 17aβ-ethynyl-17aα-hydroxy-D-homosteroid, the desired isomer. On ethynylation of D-homoetiocholane-3α-ol-11,17a-dione with sodium acetylide, a 7:1 ratio (β-OH/α-OH) was obtained. With this 17aα-hydroxy compound (I) available, the synthesis of D-homocortisone acetate was carried out in a straightforward manner as shown in the following reaction sequence.

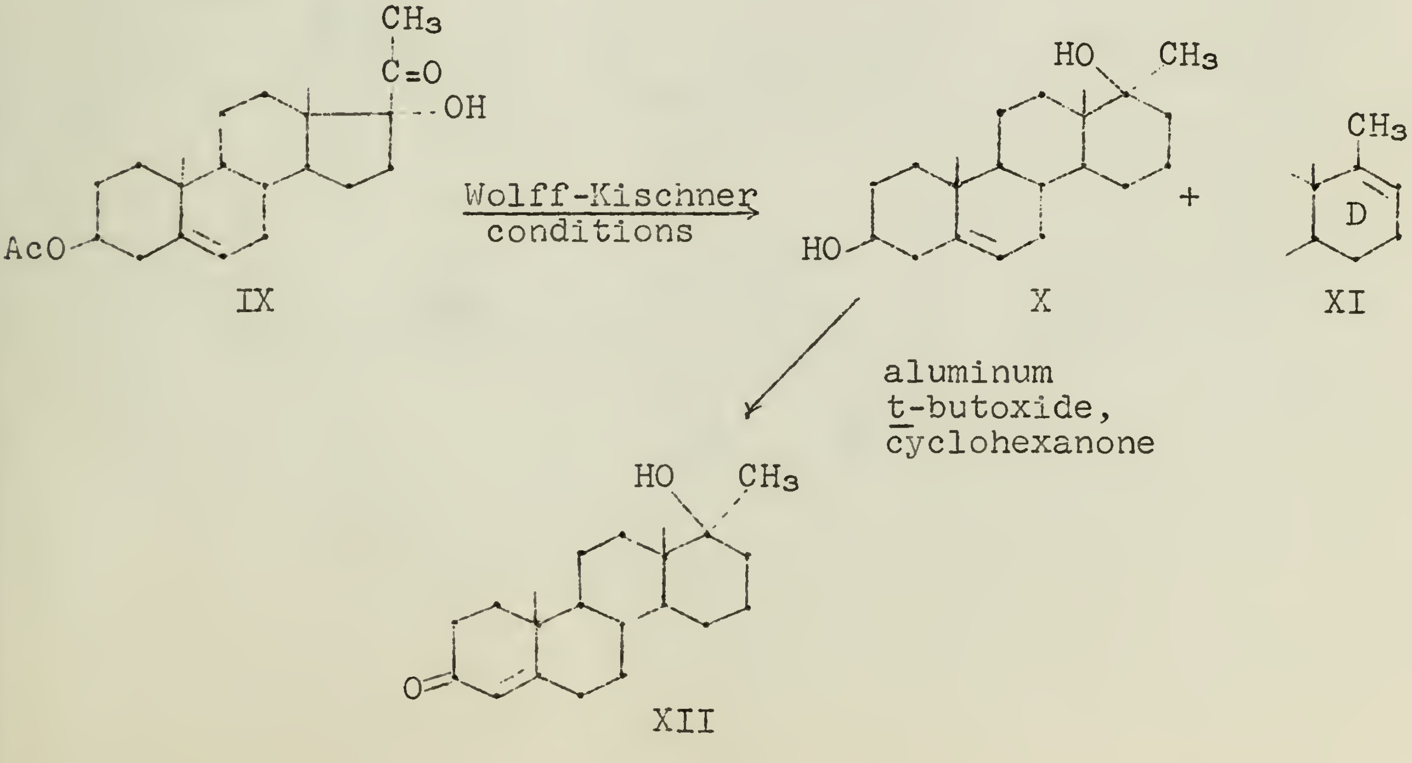


I II III



The analytical data (both elemental and spectral) were in good agreement with the structure VIII, and the compound had a glucocorticoid activity of about 1/3 that of cortisone acetate.

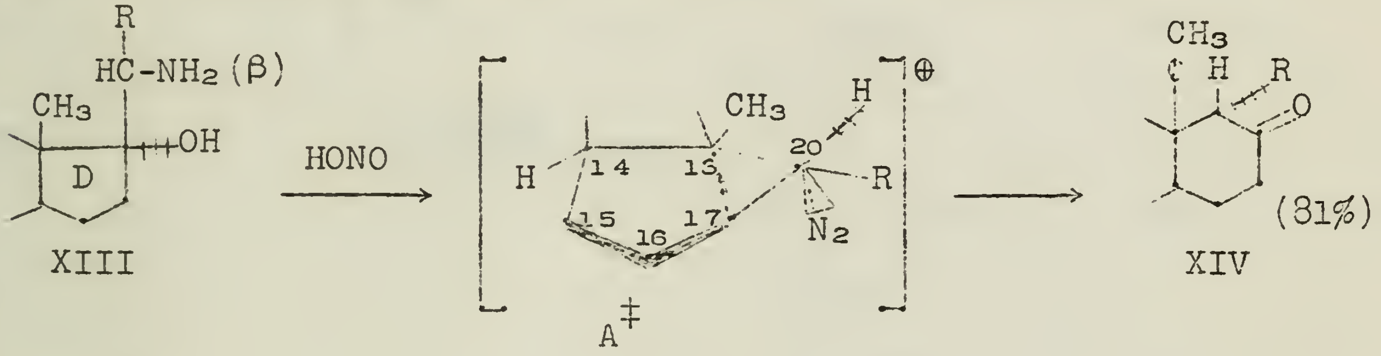
The preparation of 17aα-methyl-D-homotestosterone was not feasible by addition of methyl magnesium iodide to the appropriate 17a-ketone. The product resulting from this reaction was exclusively the 17aβ-methyl derivative (4), and was physiologically inactive. The synthesis of the isomeric 17aβ-methyl compound was carried out as shown below.

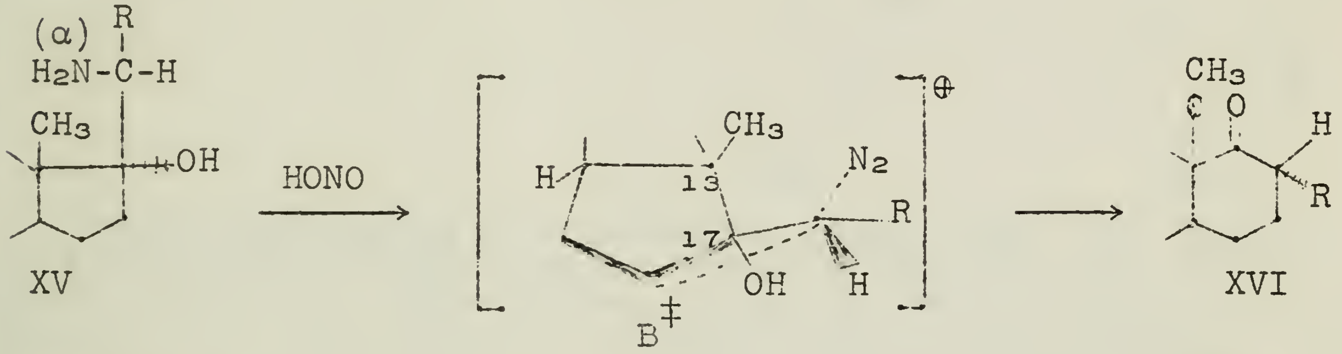


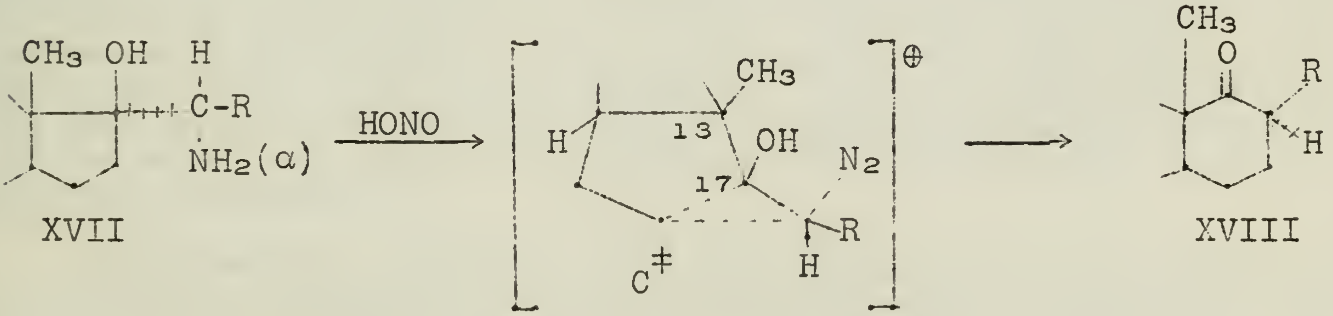
The resulting product, XII, had high androgenic activity. This fact was taken as strong supporting evidence for the assigned stereochemistry.

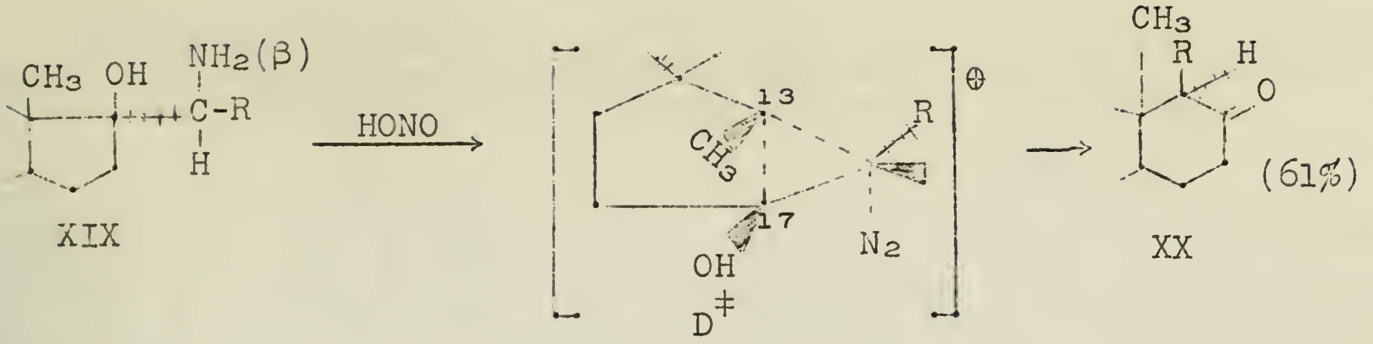
DEMONSTRATION OF REACTION MECHANISMS WITH THE RIGID D-HOMOSTEROID SYSTEMS

The mechanism of the D-homoannulation of 17-hydroxy-20-ketosteroids has been reviewed recently (6), and no attempt will be made to describe the details of the findings discussed in that report. However, another route to D-homosteroids, namely nitrosation of 17-hydroxy-20-aminosteroids (7,8,9,10), has provided a convincing demonstration of the value of mechanistic inferences in elucidation of the structures of complex molecules (11,12,13). Curtin (14) has demonstrated that the course of the nitrous acid deamination of amino alcohols is quite dependent on the amount of steric strain in the transition state. The reaction was therefore quite suitable for the exploration of steric factors operating in the environment of C-17 and -20 of a 17-hydroxy-20-amino steroid molecule (13). Consideration of the accepted mechanism for ring expansion during the Demjanov rearrangement led Ramirez to the following predictions.

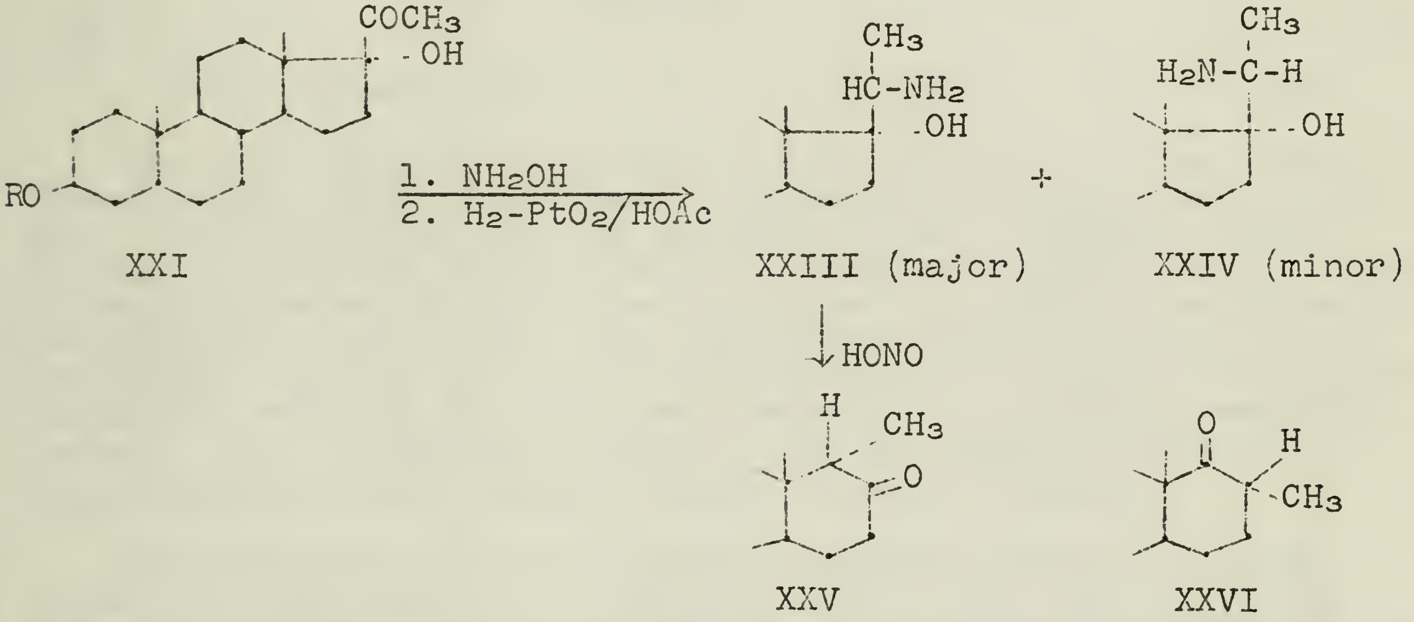








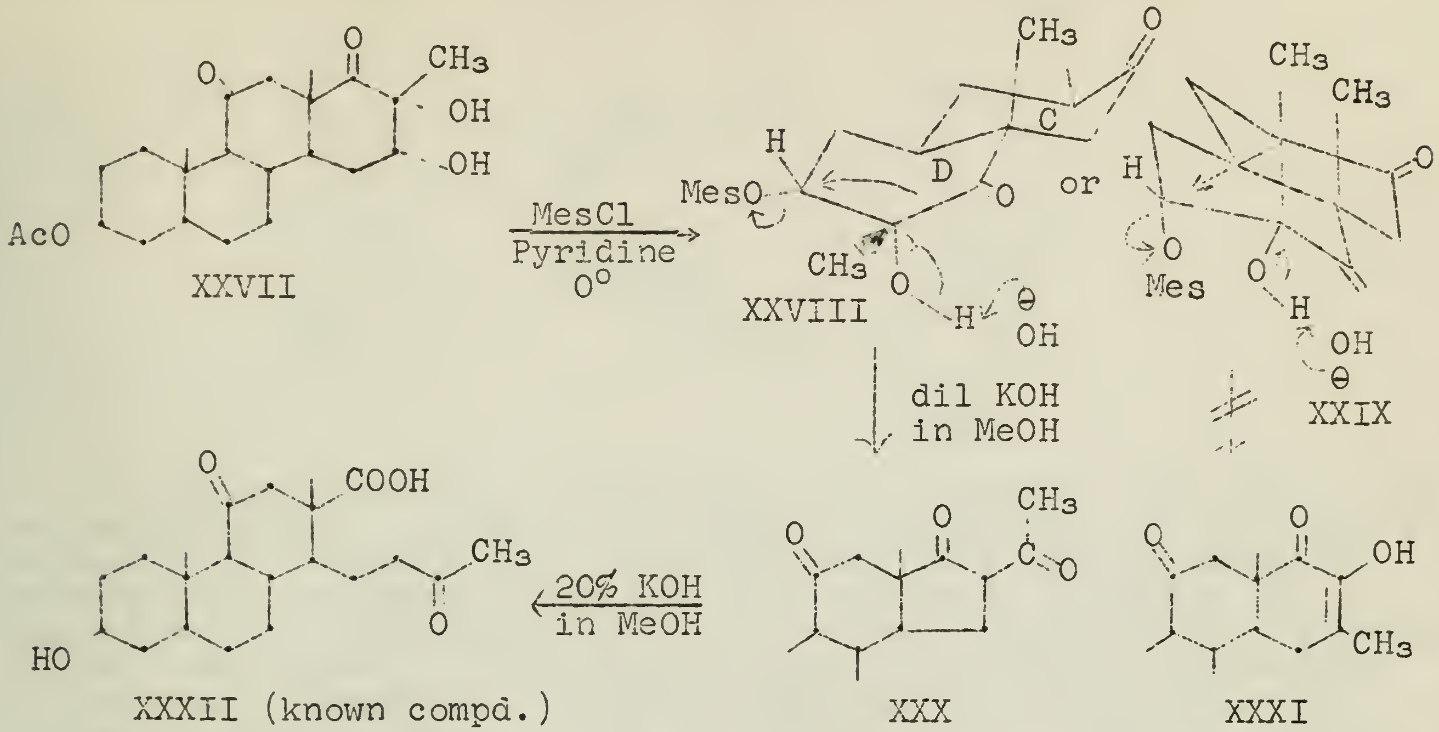
On the basis of the mechanistic considerations outlined above, the structures and configurations of the D-homosteroids obtained when the reactions were actually run were taken as direct evidence for the configurations at C-20 in the starting amino alcohols. Ramirez (12,13) prepared the two pairs of isomers (XIII and XV, and XVII and XIX) and assigned the configurations shown. The reaction sequence shown indicates the chemistry involved for elucidation of the stereochemistry of one of the isomers. Another, XIX, was studied in a parallel manner.



The D-homosteroid from the major product, XXV, was found to have a reactive methylene group, which is possible only if the keto group is at C-17. When treated with base, XXV rapidly isomerized via the 16-17 enol to give a compound with the same empirical formula and chemical properties, but different physical properties. The inference made by Ramirez (13) was that the 17a-methyl group must have been α and that it rearranged to the more stable β-configuration. [On the other hand, XXVI was stable to base and did not have an active methylene group, and was therefore assigned the 17α-methyl-17a-keto-structure.]

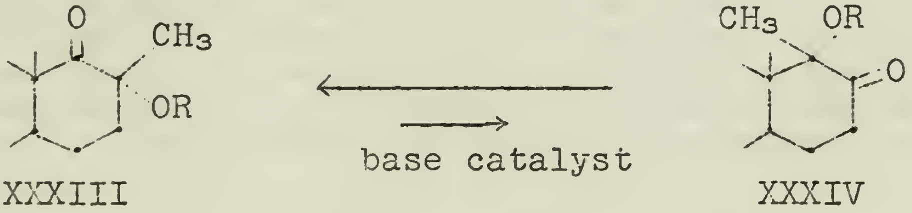
Experiments by Wendler, Taub and Slates (11) on the deamination of 17-hydroxy-20-amino-21-norpregnanes indicated an apparent lack of specificity in the reaction, since both 17α- and 17β-hydroxy-20-amino compounds gave the same mixture of 17- and 17a-ketones. In both cases, there was a ratio of 1 part 17-ketone to 6 parts 17a-ketone. If Ramirez's mechanism is correct, then it must be assumed that transition states such as B and C (See drawings above where R = H.) are more favorable relative to A and B. "The difference between them, however, is not obvious from models, but may be due to the inherent stability of the C-13-17 bond (equatorial to ring C)." (13).

Mechanistic evidence for a boat conformation of the D ring in the highly substituted steroid XXVII has been obtained by Wendler (15). The following reaction shceme summarizes his findings.

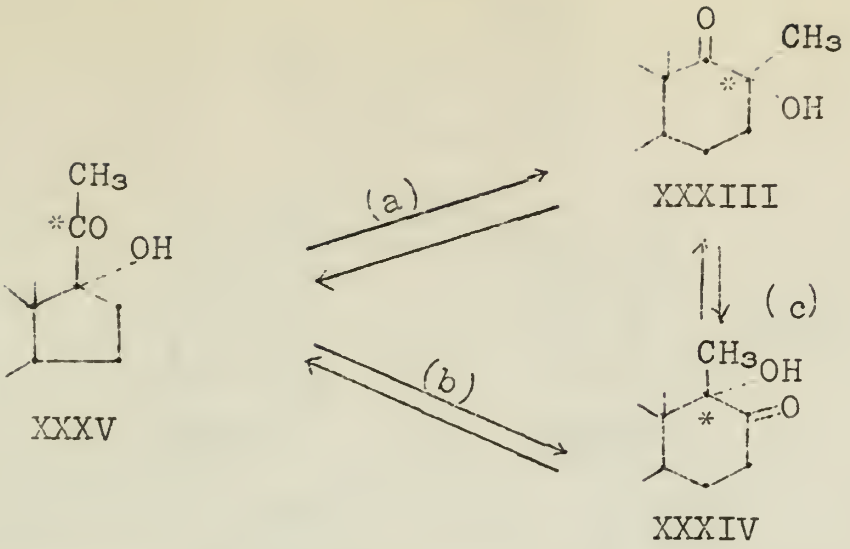


The diol XXVII was prepared by acid treatment of the known 16, 17-α-epoxide. Methanesulfonation (mesylation) of the diol under mild conditions gave only the mesylate of the secondary alcohol. If this 16-mesyloxy derivative had a chair conformation, as in XXIX, it would be expected on the basis of previous work to rearrange to the diosphenol XXXI (16). The compound isolated had none of the properties expected for the diosphenol and was assigned the structure XXX on the basis of its infrared spectrum [$\lambda\lambda_{max}$ 1740 (5-membered ketone), 1710 (6-membered ketone), 1690 and 1620 (β-diketone)]. Basic cleavage of XXX leads to XXXII, a known compound.

The existence of an equilibrium between ketols (in the Favorskii rearrangement, for example) and the ease with which the isomerization was produced by reagents such as boron trifluoride and aluminum *t*-butoxide led some French workers to the study of the ketols XXXIII and XXXIV (17).



These ketols did, in fact, appear to constitute an equilibrium system. Compound XXXIV is partially converted to XXXIII by treatment with an excess of *t*-butoxide ion. The authors felt that this was the first evidence for a "methyl migration" of this type; however, similar transformations had been previously demonstrated by Wendler (18). The relative quantities of the two ketols formed from the corresponding 17α-hydroxy-20-keto-steroid depended on the amount of isomerizing agent used. (See reaction sequence below.)



In the presence of a large excess of t-butoxide, only 10% of the rearranged product was XXXIV, but when a limited quantity of reagent was used, 25% of the D-homo derivative was the 17-ketone (XXXIV). Consequently, an excess of reagent was assumed to isomerize the 17-keto-17aα-ol to the 17a-keto-17α -ol, and the equilibrium (c) appears to favor the latter. A reasonable explanation of this observation is that the intermediate aluminate compounds tend toward the more stable disposition of the bulky $-O-Al(OR)_2$ group. The stable conformation would then be the 17α-hydroxy (equatorial) rather than 17aα (axial).

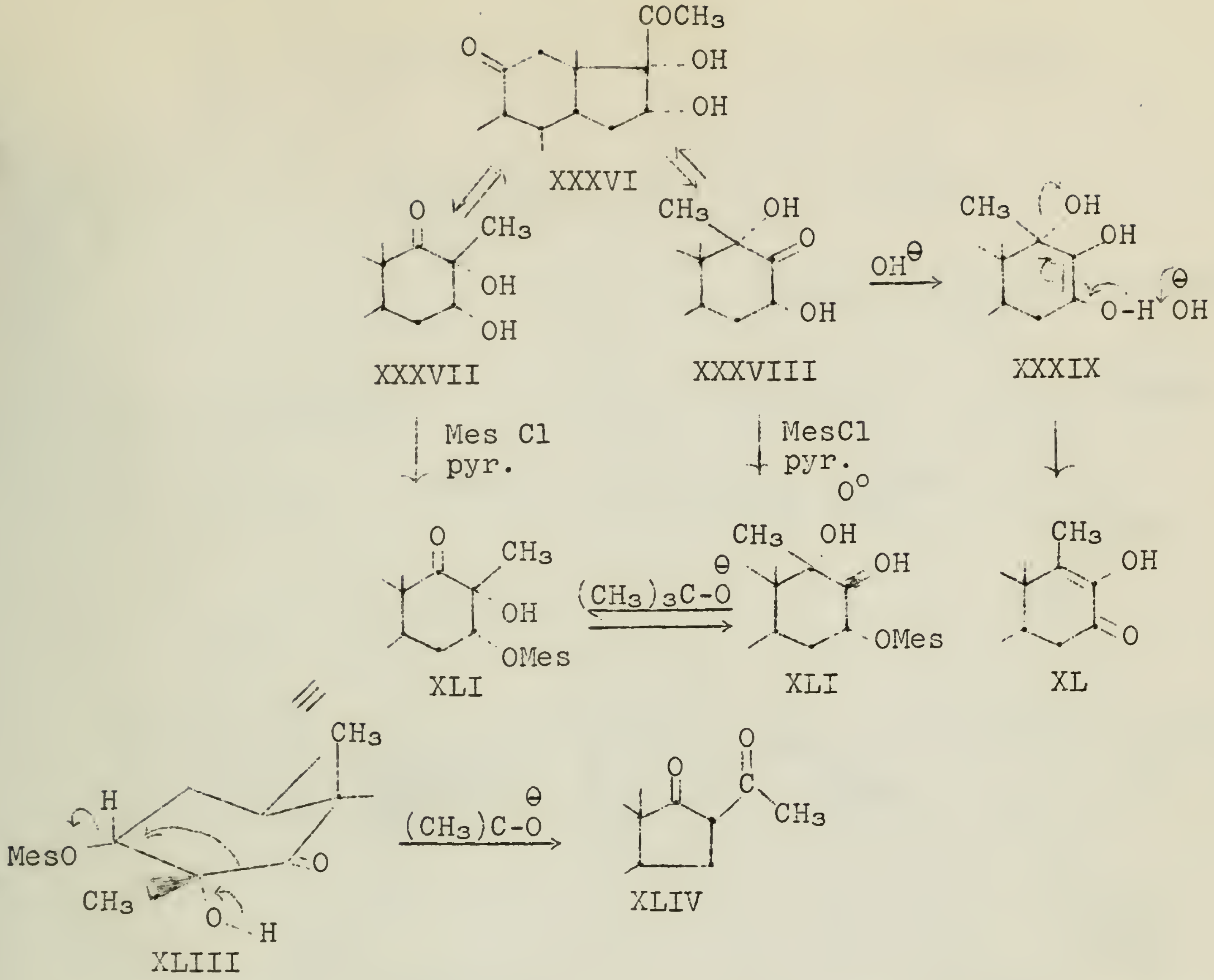
The isomerization of XXXIII and XXXIV, a priori, can go by two mechanisms:

1. Ring contraction to an intermediate such as XXXV and thence to XXXIII.

or 2. Direct methyl migration from C-17 to C-17a and vice versa.

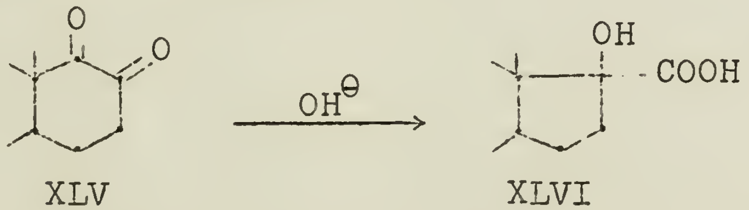
Studies with isotopically labelled C-20 (XXXV) in a large excess of t-butoxide gave the ketol XXXIII with the label only at C-17 (19). In order to explain this result, one of the equilibria indicated in the reaction scheme must be discarded. Preliminary experiments by Elphimoff-Felkin and Skrobek (17) have shown that equilibrium (b) is possible. It was therefore reasonably concluded that the methyl migration route (c) for the reaction is impossible, since it would lead to randomization of the label between C-17 and C-17a. The mechanism of isomerization of XXXIV to XXXIII probably involves intermediary D-ring contraction and then expansion. This mechanism readily accommodates the recent observations of Wendler (20).

The driving force for these reactions was considered to be the eventual collapse of each system to its stable enolate. When the 16-mesylate derivatives were made, there was no possibility for an intermediate enediol such as XXXIX, and the compounds rearranged by the elimination of mesyloxy anion and ring contraction to the 16-acetyl-17-keto-steroid (XLIV).



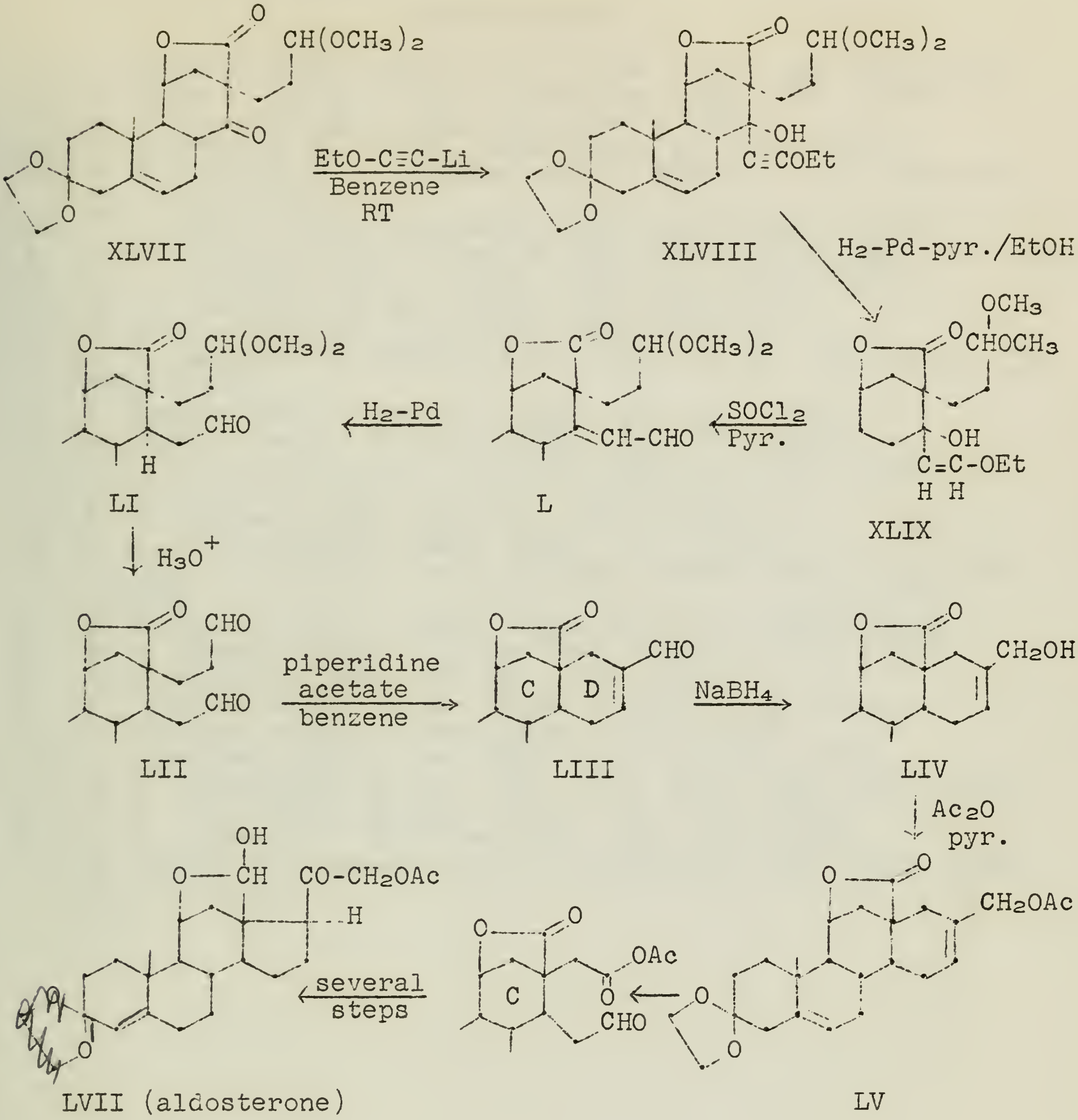
RECENT ADVANCES IN THE TOTAL SYNTHESIS OF STEROIDS WITH D-HOMO-STEROIDS AS INTERMEDIATES

Georgian and Kundu (21,22) have recently shown the feasibility of converting appropriately substituted D-homo compounds to steroids with a five-membered ring. Thus, a 17,17a-diketo-D-homosteroid (XLV) was attacked at the conformationally preferred 17a-ketone and underwent a stereospecific benzylic acid rearrangement to the α-hydroxy acid shown (XLVI).



The mechanistic considerations which led to the assignment of structure for the α-hydroxy acid (XLVI) were discussed in a recent seminar by Sheppard (23).

A new total synthesis of aldosterone (LVII) was made possible by the synthesis of a D-homo compound LV (24,25). The latter could be converted to a derivative LVI similar to those prepared by Johnson (26) and Reichstein (27).


CH(OCH3)2
EtO-C≡C-Li
Benzene
RT
XLVII
CH(OCH3)2
OH
C≡COEt
XLVIII
H2-Pd-pyr./EtOH
CH(OCH3)2
CHO
H
LI
H2-Pd
CH(OCH3)2
CH-CHO
L
SOCl2
Pyr.
OCH3
CHOCH3
OH
C=C-OEt
H H
XLIX
H3O+
CHO
CHO
LII
piperidine
acetate
benzene
CHO
C
D
LIII
NaBH4
CH2OH
LIV
Ac2O
pyr.
OH
CH
CO-CH2OAc
H
several
steps
LVII (aldosterone)
OAc
C
CHO
CH2OAc
LV

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STEREOSPECIFIC, FREE RADICAL AND NUCLEOPHILIC, ADDITIONS TO ACETYLENES

Reported by C. D. Mitchell May 25, 1959

INTRODUCTION

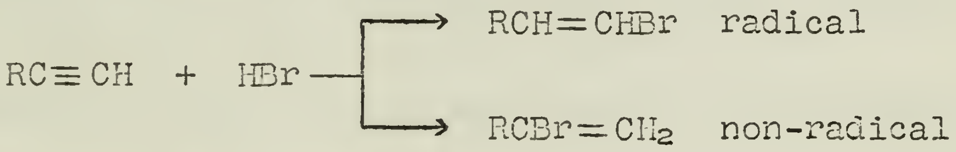
While the orientation and the stereochemistry of additions to acetylenes have been studied in detail for hydrogen (1) and carbon monoxide (2,3), and the electrophilic addition of the halogens and hydrogen halides (4), only recently has the stereospecificity of free radicals and nucleophilic agents toward the acetylenic triple bond been reported.

FREE RADICAL ADDITIONS

In 1939 Walling, Kharasch, and Mayo (5) reported the free radical addition of HBr to 2-butyne. The reaction was taken to completion by excess HBr and *d,l*-2,3-dibromobutane contaminated by a small amount of 2,2-dibromobutane (from competing ionic addition) was obtained. The *d,l*-2,3-dibromobutane could have resulted from two successive *trans* (or *cis*) additions. Motivated by this report Skell has recently investigated the stereochemistry involved in free radical additions to acetylenic compounds. Almost simultaneously other reports of apparently stereospecific radical additions to acetylenes have appeared in the literature.

ORIENTATION AS AN INDICATION OF MECHANISTIC PATH

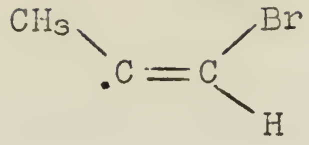
The addition of HBr to terminal acetylenes in the presence of radical inhibitors and/or Lewis type acids produces $RCBr=CH_2$ and $RCBr_2CH_3$, while the addition of HBr to terminal acetylenes in the presence of peroxides has been reported as giving a mixture of *cis* and *trans* isomers. Thus the mechanism by which the HBr addition reaction proceeds can be determined by the position or orientation of the bromine in the adduct (6).



THE STEREOSPECIFIC FREE RADICAL ADDITIONS OF HBr

Skell (6) has observed the stereospecific *trans* addition of HBr to propyne under illumination and in the liquid phase (-78° to -60°C.). The only products formed in significant amounts were *cis*-1-bromo-1-propene and 1,2-dibromopropane. The isomeric substances, *trans*-1-bromo-1-propene, 2-bromopropene and allyl bromide, could not be detected. He reports that the gas phase reactions are markedly accelerated by light and oxygen; however, the stereochemistry of the gas phase addition is obscured by the rapid equilibration of the 1-bromo-1-propenes. In the gas phase, at equilibrium, the *cis* to *trans* ratio is 4.14. Propyne is a particularly good acetylene for determining the stereochemistry of addition; for, if *trans* addition does occur, it involves a sterically compressed radical, and thus, an indication of the high degree of stability of the intermediate

radical (I) is obtained.

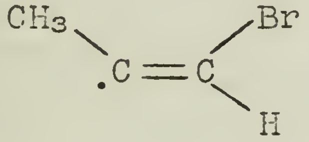


I

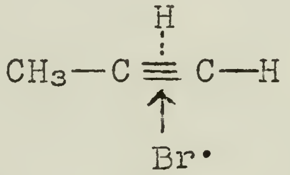
The *cis* and *trans* 1-bromo-1-propenes were distinguished through their infrared spectra and retention times in vapor phase chromatographic separations.

Under reaction conditions similar to those employed in the HBr addition to propyne, undecynoic acid yields 11-bromo-10-undecenoic acid (m.p. 18.6°C.). Since from alkaline dehydrobromination of 10, 11-dibromoundecanoic acid a small amount of 11-bromo-10-undecenoic acid (m.p. 41°C.) has been reported, *trans* configuration might be assigned to this acid and *cis* configuration to the 18.6° acid. Thus, *trans* addition of HBr is again inferred.

The liquid phase results can be explained by either of two hypotheses: (1) addition of a Br· atom produces a stable *cis* radical or (2) reaction occurs by addition of Br· to a propyne-HBr complex, closely followed by transfer of the H atom or the reaction is termolecular (propyne, HBr, and Br·).



(1)



(2)

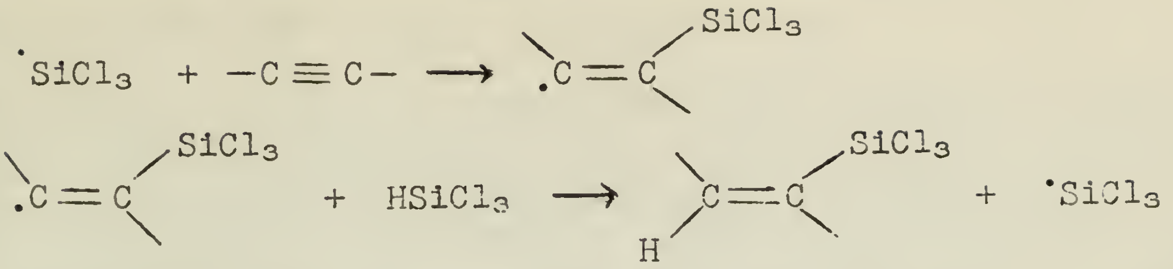
Ramsey (7) has concluded from spectroscopic analysis that in the ground state $H-\dot{C}=O$ is bent (120°) and that an electronic state lying 23 Kcal. above the ground state is linear. Thus, considerable credence is given to the possibility that vinyl radicals have structural parameters similar to the parent olefin.

THE STEREOSPECIFIC FREE RADICAL ADDITION OF SILICOCHLOROFORM

Benkeser has investigated the stereochemistry of the addition of silicochloroform to three aliphatic 1-alkynes (1-pentyne, 1-hexyne, and 1-heptyne) and phenylacetylene (8). The reactions were catalyzed by either benzoyl peroxide or platinized charcoal. In the case of peroxide catalysis stereospecific *trans* addition (producing *cis* olefins) was shown to occur by the comparison of the infrared spectra of the adducts with those of authentic compounds. In like manner platinized charcoal was shown to give stereospecific *cis* addition (producing *trans* olefins). The stability of the *cis* and *trans* isomers under the reaction conditions was demonstrated.

In the event of peroxide catalysis a radical chain mechanism is probable.

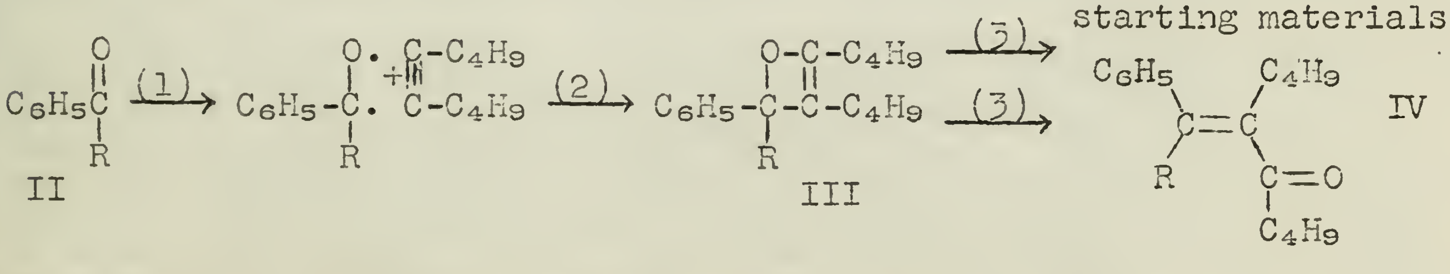
$HSiCl_3$ + peroxide $\longrightarrow$ $\cdot SiCl_3$



The stereospecific trans addition noted in the presence of peroxide is in accord with the observations made by Goering and coworkers (9) on radical-olefin additions. The reason for the stereospecificity in this instance probably is the rigidity of the radical intermediate formed in the reaction. It has been found, for example, that certain other radical additions, in which the radical intermediate is not rigid, are non-stereospecific (10). The stereochemistry of the platinum-catalyzed addition is of special interest. It has been suggested that these additions are ionic in nature. The Si-H bond may be polarized on the catalyst so that the H becomes negative and the Si positive ($\overset{-\delta}{H}\cdots\overset{+\delta}{Si}\leq$). The polarized form then adds to the olefin from one side only in a strictly cis fashion.

THE STEREOSPECIFIC FREE RADICAL ADDITION OF AROMATIC CARBONYLS

Büchi (11) has condensed benzaldehyde and acetophenone with 5-decyne by irradiation with a mercury resonance arc to obtain unsaturated ketones in approximately 13% yields. The products have been characterized by ultraviolet and infrared spectroscopy, reduction with $NaBH_4$, and synthesis by unambiguous routes. The unsaturated ketones produced in the photochemical process appear to be a mixture of cis and trans isomers, but complete separation has not been attained. Because the infrared spectra of the synthetic ketones, of known trans configuration, were nearly the same before and after prolonged irradiation it was indicated that the photochemical equilibrium mixture contained mainly trans isomer. The authors postulate that the most reasonable scheme to rationalize the formation of the alpha, beta-unsaturated ketones seems to be (1) conversion of the aromatic carbonyl compound (II) to the biradical triplet state by absorption of light, followed by (2) formation of the corresponding oxetenes (III) by a stereospecific cis addition and (3) decomposition of these intermediates to either products (IV) or starting materials: R=H or CH_3



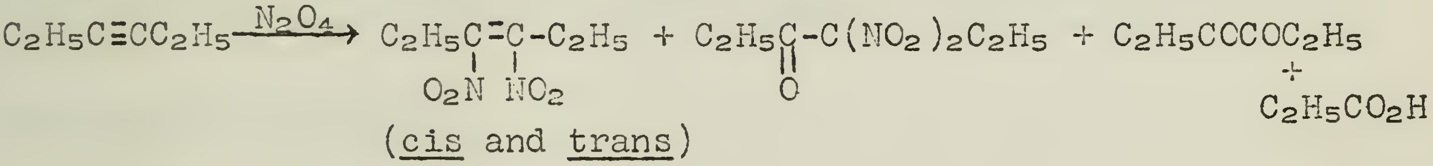
An attempt has been made to isolate III, but no evidence for its presence in the products of the reaction could be obtained. The conversion of the aromatic carbonyl group to the biradical triplet state would seem to be energetically unfavorable. The excitation of the carbonyl group to the lower energy singlet state, followed by its addition to the triple bond to form the cyclic intermediate (III) in

one step, would seem to be a more logical explanation.

THE STEREOSPECIFIC FREE RADICAL ADDITION OF N_2O_4

The addition of N_2O_4 to alkynes was first believed to occur by a heterolytic addition ($NO_2^-NO_2^+$) process. Present evidence indicates, however, a free radical mechanism; for, in the analogous reactions of N_2O_4 with olefins (reaction conditions similar to N_2O_4-alkyne reaction conditions) the operation of a free radical mechanism has been well substantiated (12). It may also be noted that if a N_2O_4-alkyne reaction is run in the presence of I_2, the iodine is captured by an apparent intermediate nitrovinyl free radical. The capture of the iodine by an intermediate does not, however, assure that the intermediate was a free radical, for a chain mechanism involving the I^+ ion could just as easily be in operation.

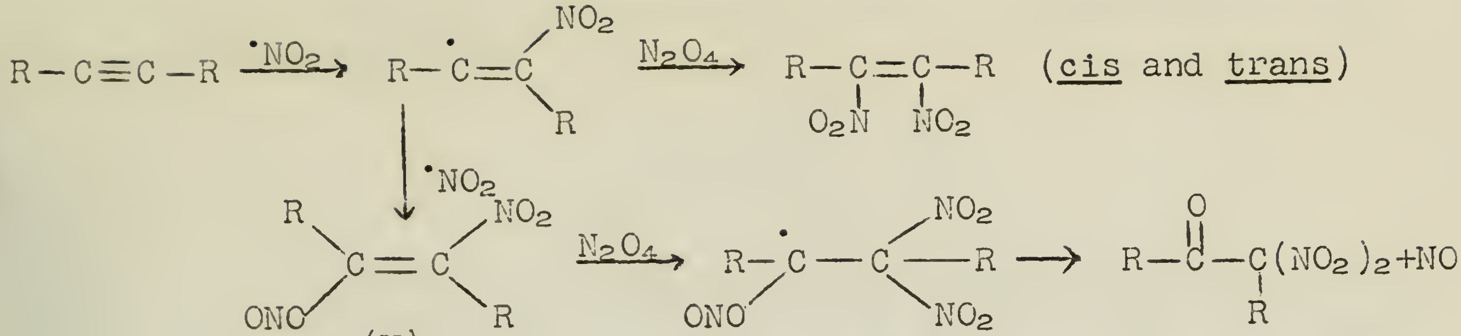
The reaction of 3-hexyne with N_2O_4 (13) was found to be of much greater complexity than a simple addition to produce dinitroölefins; the instability of the mixtures was apparently due to the formation of minor reactive products. In all, five components of the mixture obtained from N_2O_4 and 3-hexyne were identified: propionic acid (6%), dipropionyl (16%), *cis* and *trans*-3,4-dinitro-3-hexene (4.5% and 31%, respectively), and 4,4-dinitro-3-hexanone (8%).



$$C_2H_5C{\equiv}CC_2H_5 \xrightarrow{N_2O_4} \underset{(\textit{cis}\text{ and }\textit{trans})}{\underset{O_2N\ \ NO_2}{C_2H_5C{=}C{-}C_2H_5}} + \underset{O}{C_2H_5\overset{}{C}}{-}C(NO_2)_2C_2H_5 + \underset{C_2H_5CO_2H}{\underset{+}{C_2H_5COCOC_2H_5}}$$

Treatment of 2-butyne with excess N_2O_4 in ether at 0° produced two isomeric dinitrobutenes in a ratio of 5 : 1 (total yield 41%) and smaller amounts of biacetyl and acetic acid. It was necessary to use an alkaline wash in the work-up of this reaction mixture, which undoubtedly destroyed any dinitroketone and removed some biacetyl; the results of this reaction are, therefore, subject to doubt. Reduction of the dinitrobutenes was employed in order to establish their stereochemistry. It appeared that the higher boiling, less predominant dinitrobutene was the *cis* isomer as it gave *meso*-2,3-butanediamine upon catalytic reduction. Thus, the lower boiling, predominant isomer would have the *trans* configuration. The results of the reduction are made doubtful by the recent report on the racemization accompanying the reduction of optically active nitro-compounds (14). It should be noted, however, that the reduction of the supposed *trans* compound could have eliminated this doubtfulness.

The infrared spectra of the four dinitroölefins were studied in an attempt to establish their configurations. The spectra of the definitely established *cis* and *trans* dinitrostilbenes were used as models. Two significant features may be noted: (1) *cis*-dinitrostilbene exhibits a band at 1642 cm.$^{-1}$ which is absent in the *trans* isomer; this may be attributed to the olefinic double bond, (2) the "finger print region" of the *cis* isomer is considerably more complex than that of the *trans* compound, as is to be expected because of its less symmetrical nature. By comparison, then, the lower boiling isomer obtained in the 2-butyne-N_2O_4 reaction was assigned the *trans* structure and the higher boiling isomer, the *cis* configuration. The dinitrohexenes were assigned in like manner. The free radical mechanism for the addition may be written as follows:



(V)

The above scheme represents simply a rationalization of the experimental results and says nothing about the possible intervention of other species such as nitric oxide in the reaction. The reaction of a second molecule of N_2O_4 with the nitronitrite (V) can be viewed as a concerted process with the loss of NO accompanying the addition of NO_2. At present it is not known whether dinitrites or dinitronitrites are the precursors of the diketones. Possibly, they are intermediates in the oxidation processes that produce the acid fragments. The predominance of *trans* isomer obtained in the N_2O_4-alkyne reactions just outlined might again reflect the stability of an intermediate vinyl type radical, but it is more likely explained by equilibrium. The stability of known *cis* and *trans* isomers under reaction conditions should be determined in order to clarify this point.

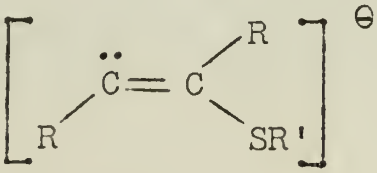
NUCLEOPHILIC ADDITION

Truce (16) has observed that in the base catalyzed addition of thiols to acetylenic compounds stereospecific *trans* nucleophilic addition occurs across the triple bond. For example, the conversion of chloracetylene and *p*-tolylmercaptoacetylene by alcoholic sodium *p*-toluenethiolate produces *cis*-1-chloro-2-(*p*-tolylmercapto)-ethene and *cis*-bis-(*p*-tolylmercapto)-ethene, respectively (17). *Trans* addition has also been noted in the addition of sodium *p*-tolylthiolate to both phenyl acetylene and 2-butyne (16). Truce's rule of *trans* nucleophilic addition finds additional support in the reaction of nucleophilic reagents with vinyl type halides. A mechanism entirely consistent with the facts can be formulated for this reaction if it is assumed that *trans* addition of the nucleophilic agent to an intermediate acetylenic compound occurs to give the ultimately observed *cis* product. A review of these reactions is available (18).

THE MECHANISM OF THE *TRANS* NUCLEOPHILIC ADDITION

If the addition reaction is stepwise there should be an intermediate configurationally stable carbanion (VII):

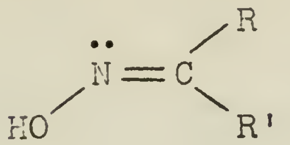
$R = CH_3$, C_6H_5, or H
$R' = p\text{-}C_7H_7$ or CH_3



VII

The indicated stereochemistry would be expected on the basis that in the transition state the negative charge (electron pair), and the negatively charged sulfur group would tend to be separated as far as possible from each other. This postulated configurational stability

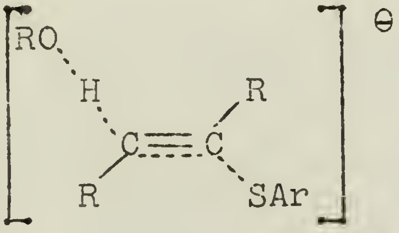
of a "vinyl" carbanion is reminiscent of the geometry of the isoelectronic oximes (VIII)



VIII

and of the retention of configuration by lithium compounds formed from vinyl halides. However, any analogy between this last result and a structurally stable carbanion is weakened by the considerable covalent character of a carbon-lithium bond.

Another route by which these stereospecific trans nucleophilic additions may be proceeding is a concerted process, involving the transition state (IX):

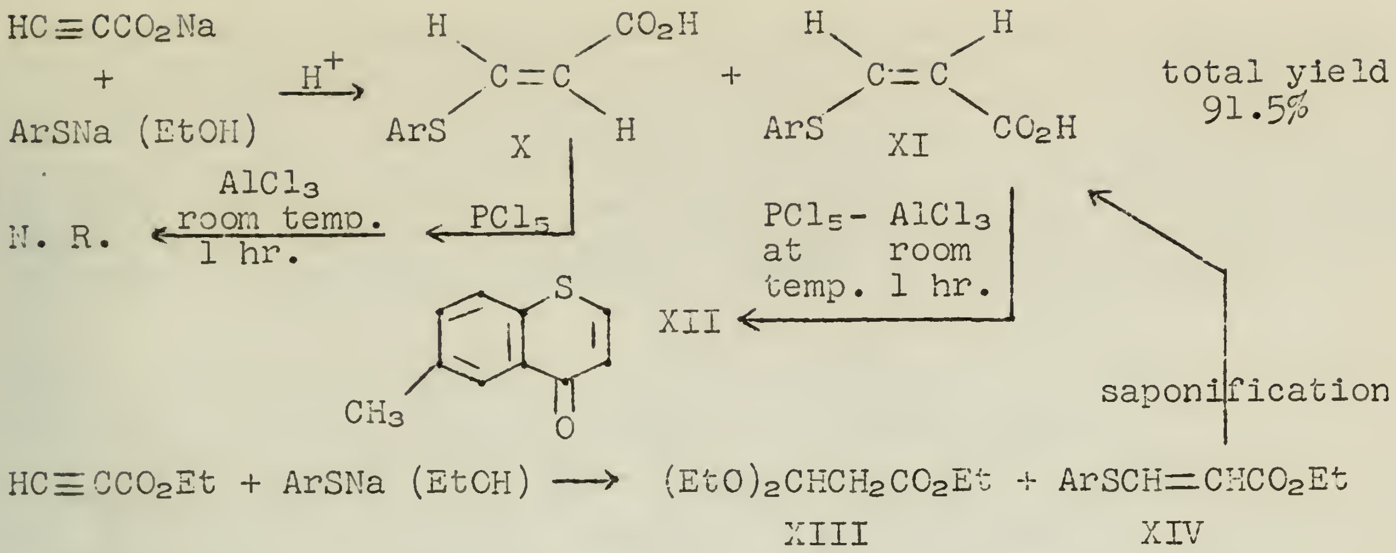


IX

AN EXCEPTION TO THE RULE OF TRANS NUCLEOPHILIC ADDITION

Addition of an ethanolic solution of p-toluenethiol containing a catalytic amount of sodium ethoxide to an aqueous ethanolic solution of sodium propiolate, either at room temperature or with external cooling, gave a combined quantitative yield of two acids, m.p. 144.5-145.5°C. (X) and m.p. 136-137°C. (XI). Both were characterized as β-p-tolylmercaptoacrylic acids on the basis of their neutral equivalents, analyses, and infrared spectra. Compound X made up 85-95% of the total product with the remainder being XI. Infrared suggested that compound X was trans-β-p-tolylmercaptoacrylic acid, and XI was the cis compound. Additional evidence for the configurational assignments made to X and XI was provided by subjecting each to PCl_5, then $AlCl_3$ for short periods at room temperature. Practically all of X was recovered unchanged; XI gave an almost quantitative yield of the cyclization product, 6-methylthiochromone (XII). Under more vigorous conditions X also cyclized, because of preliminary isomerization under the Friedel-Crafts conditions (20).

Ethyl propiolate when subjected to reaction with thiolate yielded (exothermally) two products, ethyl β,β-diethoxypropionate (XIII) and β-p-tolylmercaptoacrylate (XIV). Saponification of the latter compound gave only the cis-acid (XI). (An almost negligible amount of the trans-acid (X) was detected.) Refluxing solutions of both X and XI in alcoholic base for 24 hours resulted in no isomerization, thus precluding the possibility of an isomerization occurring during some stage of the experimental work: (Ar= p-CH_3-C_6H_4)



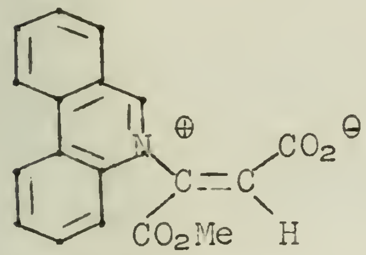
The base catalyzed addition of *p*-toluenethiol to phenyl ethynyl ketone has been performed under various conditions (20). In every case but one, only one compound was isolated in quantitative yield--with NaOEt as the catalyst and EtOH as the solvent two products were obtained ($(EtO)_2CHCH_2COC_6H_5$ and $C_7H_7SCH{=}CHCOC_6H_5$). The product common to each reaction was identified as *cis*-*p*-$CH_3C_6H_5SCH{=}CHCOC_6H_5$ on the basis of its facile oxidation to the previously identified *cis*-sulfone.

The violation of the rule of *trans* nucleophilic addition by sodium propiolate is apparently associated with the presence of a negatively charged group; for as has just been pointed out, ethyl propiolate, phenyl ethynyl ketone and for that matter other acetylenes which bear uncharged substituents obey the rule. As previously mentioned, the explanation for the usual *trans* nucleophilic additions is based on coulombic repulsion between the attacking negatively-charged thiolate ion and the pair of electrons being displaced from the triple bond, thereby forcing the displaced electron pair to the *trans* position where it abstracts a proton from the solvent. However, in the case of propiolate ion a competing coulombic repulsion can exist between the negatively-charged carboxylate substituent and the thiolate group. This repulsion would tend to force these groups into a *trans* relationship and thus cause the over-all addition to proceed *cis*. Additional support to this interpretation is found in the report that ammonium sulfite adds to salts of propiolic acid to give *trans*-β-sulfoacrylic acid (*i*.*e*., *cis* addition) (19).

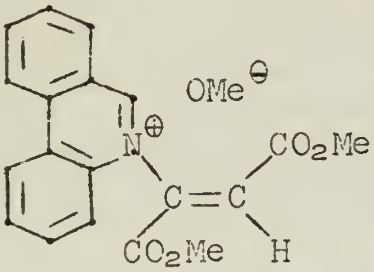
A POSTULATED EXTENSION OF THE PRINCIPLES GOVERNING TRANS NUCLEOPHILIC ADDITION

The rule of trans nucleophilic addition should be applicable only to negatively-charged nucleophilic agents (20); for with uncharged nucleophilic agents *e*.*g*. amines, the attacking grouping would be developing a positive charge in the transition state to addition and hence would tend to bring the displaced electron pair into a *cis* arrangement relative to itself. While Jones and Whiting (21) have provided some evidence in support of the predicted *cis* addition of amines, recent evidence indicates a *trans* addition. Acheson (22) has reported that phenanthridine and methyl acetylenedicarboxylate combine in anhydrous methanol to give a 76% yield of the yellow methoxide (XIX). Crystallization of this compound (XIX)

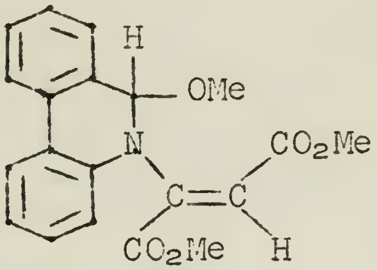
from methanol containing 5-15% water gave exclusively and irreversibly the betaine (XVIII or its isomer); whereas if the water content exceeded 15%, the carboxyphenanthridinium hydroxide (XXI) was formed. If the reaction is carried out in the presence of 5-15% and greater than 15% water, the corresponding compounds are obtained directly. Acheson (23) has also observed that acridine added to methyl acetylenedicarboxylate gives largely 10-*trans*-1:2-dimethoxycarbonylvinyl) acridinium methoxide along with a little of the *cis* isomer.



XVIII

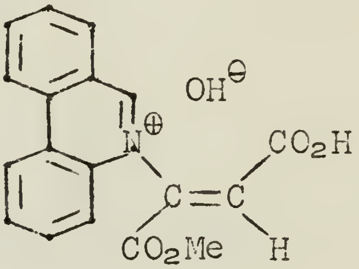


XIX



XX

XXI



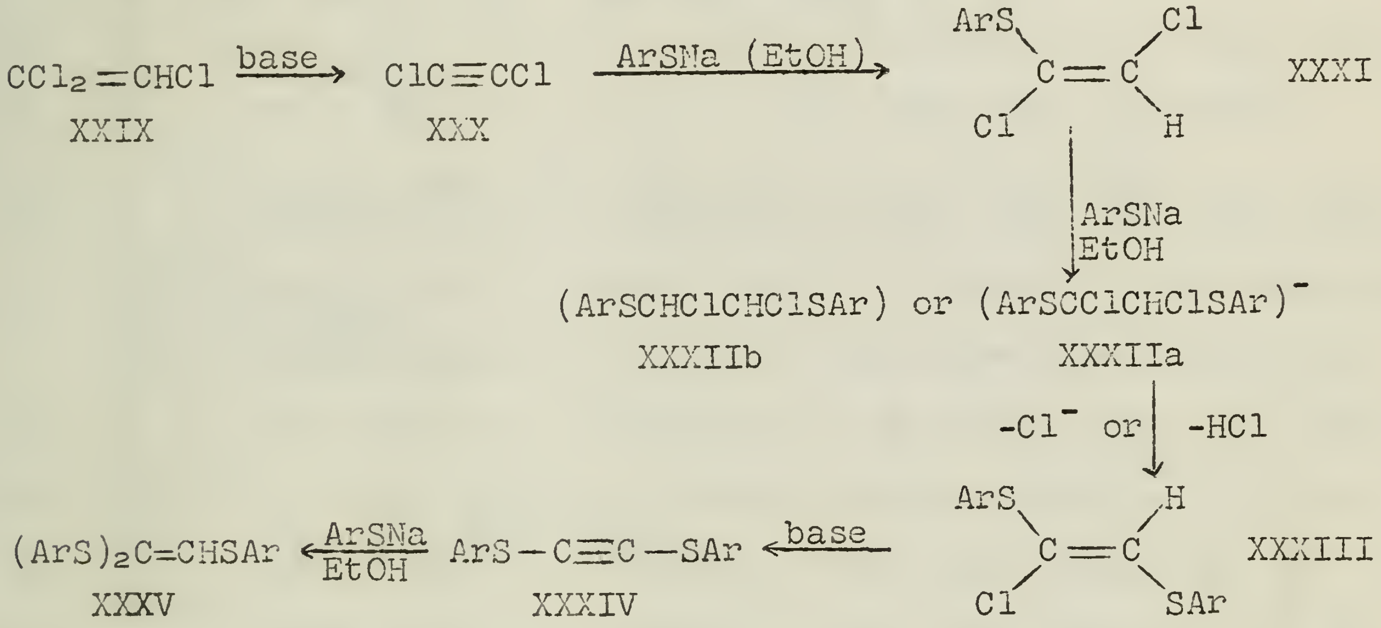
Interconversions of the three XIX, XX, and XXI and degradations to phenanthridine, phenanthridone, and toN-(1:2-*trans*-dicarbomethoxyvinyl)-phenanthridone, provide structural proofs. Conversion of the last compound into an anhydride followed by hydrolysis gave the isomeric acid, which can only be the *cis* isomer. (*i.e.* Oxidation of the betaine (XVIII) with alkaline ferricyanide gave N-(*trans*-1:2-dicarboxyvinyl)-phenanthridone. In refluxing acetic anhydride this acid was converted into the anhydride, which on hydrolysis gave the isomeric N-(*cis*-1:2-dicarboxyvinyl)-phenanthridone, thus establishing the stereochemistry of these compounds and proving that the original condensation gave *trans*-products as largely the case also in the acridine series.)

THE APPLICATION OF THE RULE OF TRANS NUCLEOPHILIC ADDITION IN POSTULATING MECHANISMS FOR THE REACTION OF VINYL TYPE HALIDES WITH NUCLEOPHILIC AGENTS IN THE PRESENCE OF BASE

Truce (24) has described two different mechanisms by which nucleophilic agents may react with halogenated ethylenes; (1) either initial *beta*-elimination to form an acetylenic intermediate followed by nucleophilic addition or (2) initial nucleophilic addition to form a saturated intermediate or an incipient carbanion followed by elimination of HX or X^-, respectively. The path followed is determined largely by the basicity of the reagent and the tendency of the halo-ethylene system to undergo dehydrohalogenation on the one hand, and by the nucleophliicity of the reagent and the "electrophilicity" of the vinyl grouping on the other hand. By way of illustration, the base-catalyzed reaction of *p*-toluenethiol (25) with the readily dehydrohalogenated *cis*-dichloroethylene proceeds by initial elimination; whereas similar treatment of the more polar and much less readily dehydrohalogenated vinylidine chloride (26) gives

initial nucleophilic addition although the same final product, *cis-bis*-(*p*-tolylmercapto)-ethene, is obtained. A more detailed review of these two reactions is available (18).

Truce has recently extended the series of compounds investigated to trichloroethylene (27). If trichloroethylene (XXIX) is allowed to react with sodium *p*-toluenethiolate in the presence of sodium ethoxide for an extended reaction time, a solid product identified as 1,1,2-tris-(*p*-tolylmercapto)-ethene (XXXV) is obtained in 97% yield. It has been observed that a mixture of *p*-toluenethiol and its sodium salt does not react with trichloroethylene (XXIX), whereas sodium *p*-toluenethiolate in the presence of sodium ethoxide gives an 81% yield of 1,2-dichloro-1-(*p*-tolylmercapto)-ethene (XXXI). The required presence of base suggests that the initial step in the reaction is dehydrohalogenation or that mechanism number (1) is being followed. The reaction scheme may then be postulated as follows:



The stereospecificities observed in the preceeding reactions may be accounted for by supposing *trans* elimination, *trans* nucleophilic addition and the *cis*-effect (28).

Dichloroacetylene (XXX) was independently synthesized by the vapor phase dehydrohalogenation of trichloroethylene over a KOH-calcium oxide mixture, and a mixture of *p*-toluenethiol and its sodium salt was added to an ether-ethanol-dichloroacetylene solution. The product of the reaction had an infrared spectrum identical with that of the product, 1,2-dichloro-1-(*p*-tolylmercapto)-ethene (XXXI), of the reaction of thiolate with trichloroethylene. XXXI has been assigned the *trans* structure on the basis of the rule of trans nucleophilic addition, and this is supported by its extremely sluggish behavior in dehydrohalogenation (25). *Trans*-1,2-dichloro-1-(*p*-tolylmercapto)-ethene (XXXI) may be converted to XXXV in 78% yield by treating it with an excess of sodium *p*-toluenethiolate. If, on the other hand, it is treated with *p*-toluenethiol and a catalytic amount of sodium *p*-toluenethiolate, 1-chloro-1,2-di-(*p*-tolylmercapto)-ethene (XXXIII) can be isolated. Presumably this arises by way of an initial nucleophilic attack to form an incipient carbanion or symmetrical intermediate (XXXIIa or b). If *trans*-1-chloro-1,2-di(*p*-tolylmercapto)-ethene (XXXIII) is treated with *p*-toluenethiol and a deficiency of base, no reaction occurs and 85% of XXXIII is

recovered. However, when this intermediate is treated with sodium p-toluenethiolate and an excess of base, the final product is isolated in 97% yield. Since an excess of base is again observed to be necessary, an elimination-addition reaction is suggested. Furthermore, XXXIII is readily dehydrohalogenated to bis-(p-tolylmercapto)-ethyne (94% yield), which reacts with p-toluenethiol in 90% yield, to produce 1,1,2-tris-(p-tolylmercapto)-ethene (XXXV).

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